A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DUPILUMAB AND MILK ORAL IMMUNOTHERAPY FOR THE TREATMENT OF PATIENTS WITH COW'S MILK ALLERGY

Dupilumab and Milk OIT for the Treatment of Cow's Milk Allergy

VERSION 11.0 / 10.22.2024

Study Sponsor(s): Stanford University

IND Sponsor/Number: Andrew J. Long, Pharm.D. / IND# [redacted]

Study Drug Manufacturer/Provider: Dupilumab manufactured and provided by Regeneron Pharmaceuticals. Cow's milk powder for oral immunotherapy manufactured and provided by the Stanford – SNP Manufacturing Facility

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INVESTIGATOR SIGNATURE PAGE	
Protocol: Dupilumab and Milk OIT for the Treatment of Cow's Milk Allergy	**Version/Date:** 11.0/ October 22 , 2024
Title: A phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab and milk oral immunotherapy for the treatment of patients with cow's milk allergy.	
Study Sponsor: Stanford	
IND Sponsor: Andrew J. Long, Pharm.D.	
INSTRUCTIONS: *The site Principal Investigator should print, sign, and date at the indicated location below. The original should be kept for your site records, and a copy of this signature page should be sent to:* *Andrew Long, PharmD, Stanford University*	
I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements. As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and Stanford. _____ **Site Principal Investigator (Print)** _____ _____ **Site Principal Investigator (Signature)** **Date**	

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab and milk oral immunotherapy for the treatment of patients with cow's milk allergy
Short Title	MAGIC Study
IND Number	[redacted]
Clinical Phase	Phase II
Site Locations	3 academic sites: Stanford University in California; Mayo Clinic and Phoenix Children's Hospital in Arizona
Study Objectives	**Primary objective** • To assess whether dupilumab as an adjunct to milk oral immunotherapy (OIT) compared to placebo improves desensitization and safety, defined as an increase in the proportion of subjects who pass a double-blind placebo-controlled food challenge (DBPCFC) to at least 2040 mg cumulative milk protein at week 18 **Secondary objectives** • **Clinical** o To assess the effect of dupilumab (compared to placebo) on ability to tolerate ≥1040 mg and 4040 mg cumulative milk protein at week 18 DBPCFCs o To assess the effect of dupilumab (compared to placebo) on ability to tolerate ≥1040 mg, ≥2040 mg, and 4040 mg cumulative milk protein at week 24 DBPCFCs o To compare levels of desensitization, defined as an increase in the cumulative tolerated protein dose (log transformed) of milk protein, from baseline to week 18 and baseline to week 24 DBPCFCs across treatment cohorts • **Safety** o To compare the rates and severity of OIT-induced gastrointestinal symptoms in subjects receiving dupilumab compared to placebo. o To compare the safety of each treatment cohort as measured by rate and severity of allergic and non-allergic AEs during respective study phases o To compare rates of study completion among treatment cohorts • **Exploratory and Mechanistic** o To explore the relationship between OIT-induced gastrointestinal symptoms and esophageal eosinophilia in subjects receiving dupilumab compared to placebo, if data is available o To evaluate the immunological responses associated with OIT-induced AEs and successful desensitization
Study Design	This is a phase 2, multicenter, randomized, double-blind, parallel group, 2-arm study in subjects aged 4 to 50 years inclusive who are allergic to cow's milk. The study consists of a screening period followed by a 24-week treatment period,

	which includes a 4-week run-in period with dupilumab or placebo followed by 12 weeks of treatment with dupilumab or placebo in combination with a gradual up-dosing of milk protein OIT, then followed by 8 weeks of cow's milk OIT dosing with no dupilumab or placebo. ***Screening (V1)*** After obtaining informed consent/assent, subjects will be assessed for eligibility at a screening visit. Procedures for the screening visit may be spread over one to three days. During screening visits, subjects will undergo a medical history, physical examination, and spirometry, as able, with potential skin prick test (SPT) and will be evaluated for the study eligibility criteria. During the screening visits, under monitoring by trained personnel, subjects meeting all eligibility criteria will undergo a DBPCFC to confirm milk allergy. This will consist of 6 doses of milk protein given every 15 to 30 minutes in increasing amounts up to a cumulative total of 444 mg of cow's milk protein. The doses will be 1, 3, 10, 30, 100, 300 mg (**Table 2**). Vital signs will be assessed every 15 minutes. If the study team suspects a reaction may be developing, they may exercise their clinical judgment to separate doses by up to an additional 30 minutes (1 hour maximum between doses). The placebo challenge will consist of placebo material (oat) also given in 6 doses matching that of the active challenge. Both milk protein and oat will be concealed in an age-appropriate, non-offensive food vehicle that masks the taste. If the study team suspects a reaction may be developing, they may exercise their clinical judgment to separate doses by up to an additional 30 minutes (1 hour maximum between doses). The food challenge will be stopped and appropriately treated in the occurrence of two or more objective Grade 1 (Mild) reactions involving two or more organ systems; OR a persistent Grade 1 (Mild) reaction; OR any reaction of Grade 2 (Moderate) or higher severity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. After the last dose of each DBPCFC, the subject will be monitored for at least 2 hours and discharged from the clinic when clinically stable. Subjects will be considered to have tolerated the DBPCFC and excluded from the study if they do not experience any of the criteria listed above that would result in the stopping of the DBPCFC, including at the highest dose. ***Active Run-In Phase (4 weeks, Visit 2 & 3)*** Subjects with a history of confirmed cow's milk allergy who meet all eligibility criteria at screening will undergo baseline assessments and will be randomized in a 1:1 ratio to begin receiving dupilumab/placebo every two to four weeks per age and body weight. ***Combination Therapy Phase (12 weeks, Visit 4 to Visit 10)*** *Initial Dose Escalation Day (Visit 4)* At week 4 (Visit 4), participants will undergo an initial dose escalation in clinic to determine the dose in which they will begin milk protein OIT. Dupilumab/placebo will be administered in clinic at least 30 minutes prior to the first dose of milk OIT. The initial dose escalation will consist of three doses of milk protein given every 15 to 30 minutes in increasing amounts up to a

	cumulative total of 35 mg milk protein. The doses will be 5, 10, and 20 mg protein mixed in an age-appropriate, non-offensive food vehicle (**Table 3**). The escalation may be stopped at the occurrence of any adverse event (AE) per clinician discretion. The tolerated dose at the initial escalation is defined as the highest non-cumulative dose in which the participant experienced no dose-limiting symptoms per investigator discretion. Participants will be discharged with a supply of milk OIT doses for daily home-dosing. The first dose will be taken the day after Visit 4, and the dose at which the participant will begin OIT will be the highest non-cumulative protein dose tolerated during the initial escalation (i.e. 5 mg, 10 mg, or 20 mg). Participants not tolerating at least the 5 mg dose at the initial escalation will be considered treatment failures and discontinued from the study. *Combination Therapy (Visit 4 to Visit 10)* During combination therapy (dupilumab/placebo plus milk OIT), participants will return to clinic approximately every two weeks to gradually increase their daily milk OIT dose to a maximum of 1000 mg protein daily as tolerated. Milk OIT will follow a standardized up-dosing regimen (**Table 1**). During combination therapy, dupilumab/placebo will be administered every two to four weeks in clinic at least 30 minutes prior to the in-clinic milk OIT dosing. The last dose of dupilumab/placebo given in the study will be administered at week 16 (Visit 10). ***Week 18 Double-Blind, Placebo-Controlled Food Challenge (Visits 11a & b)*** At week 18, under intensive monitoring, all subjects will undergo DBPCFCs up to 4040 mg milk protein (cumulative) and placebo to assess desensitization. The DBPCFCs will consist of 7 doses (milk protein or placebo), given every 15 to 30 minutes: 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg, and 2000 mg protein, resulting in a total challenge of up to 4040 mg milk protein (cumulative). Vital signs will be assessed every 15 minutes. Participants will receive a new kit of home OIT doses at Visit 11a at the same dose as that previously dispensed and tolerated at Visit 10. Participants will skip their daily home dose of milk OIT on DBPCFC days (Visit 11a and b), but will take their home dose on days between the DBPCFCs if the DBPCFCs are not on consecutive days. ***Washout Phase (8 weeks, Visit 10 to Visit 14a)*** Participants previously tolerating 1000 mg protein daily at Visit 10 will remain at 1000 mg, as tolerated, throughout the 8 week washout (milk monotherapy) phase. All other participants will continue to attempt dose escalations in clinic approximately every two weeks following the week 18 DBPCFCs until a maximum daily dose of 1000 mg protein, as tolerated. Those escalating to and tolerating a daily dose of 1000 mg protein daily will remain at that dose for the remaining visits. The final possible up-dosing will occur at Visit 13. ***Week 24 Double-Blind, Placebo-Controlled Food Challenge (Visits 14a & b)*** At week 24, under intensive monitoring, all subjects will undergo DBPCFCs up to 4040 mg milk protein (cumulative) and placebo to assess desensitization. The challenges and procedures are to follow those of the week 18 (Visit 11a and b) DBPCFCs detailed above. The conclusion of the second DBPCFC and Visit 14b will mark the end of the study and no further dosing will occur in participants.

Primary Endpoint	Proportion of subjects treated with dupilumab plus milk protein OIT vs placebo plus milk protein OIT who tolerate at least 2040 mg (cumulative) cow's milk protein during DBPCFC to milk at week 18
Secondary Endpoints	**Clinical** • Proportion of participants who tolerate at least 1040 mg cumulative milk protein at week 18 DBPCFC • Proportion of participants who tolerate 4040 mg cumulative milk protein at week 18 DBPCFC • Proportion of participants who tolerate at least 1040 mg cumulative milk protein at week 24 DBPCFC • Proportion of participants who tolerate at least 2040 mg cumulative milk protein at week 24 DBPCFC • Proportion of participants who tolerate 4040 mg cumulative milk protein at week 24 DBPCFC • Change in the cumulative tolerated dose (CTD) of milk protein during DBPCFC from baseline to week 18 and baseline to week 24 across cohorts as pairwise comparisons of all treatment groups ○ Due to the positive skew for the distribution of the CTD, a log transformation will be applied to reduce the skewness **Safety** • The rate and severity of OIT-induced gastrointestinal symptoms in subjects receiving dupilumab compared to placebo. Proportion of participants who have OIT-induced gastrointestinal symptoms, dupilumab compared to placebo • The rate and severity of AEs, SAEs, and safety events in each cohort • Proportion of participants completing the study among cohorts **Exploratory and Mechanistic** • Change from baseline to week 24 in the log-transformed minimum concentration of milk protein which activates basophils, comparison between dupilumab and placebo • Percent change from baseline to week 24 in milk-specific and total IgE and milk-specific and total IgG4, comparison between dupilumab and placebo • Percent change from baseline to week 24 in milk SPT response, comparison between dupilumab and placebo • Proportion of subjects experiencing esophageal eosinophilia, dupilumab compared to placebo, if data is available
Procedures and Assessments	The efficacy of dupilumab will be assessed by DBPCFC at week 18 (primary and secondary) and week 24 (secondary). Overall safety will be assessed by monitoring/evaluation of allergic reactions, treatment-emergent adverse events (TEAEs), physical examinations, and vital signs at pre-specified time points.
Study Duration	The duration of the study for a subject is approximately 24 weeks, excluding the screening period.

Population	**Sample Size** The accrual objective is 116 subjects, 58 and 58 for the dupilumab and placebo treatment groups, respectively, with a history of confirmed milk allergy will be enrolled at 2 academic sites in the US. **Target Population** Male and female subjects aged 4 to 50 years, inclusive, with a history of cow's milk allergy confirmed by milk SPT and/or milk-specific IgE, and by the level of milk protein tolerated during DPBCFC to milk.

Treatment Description	**Study Drug: Dupilumab - Dose/Route/Schedule**
	
	• Participants aged 4-5 years old:
	  ○ ≥5 to <15kg will receive dupilumab 200 mg or placebo SC every 4 weeks following a loading dose of 400 mg on day 1 (Visit 2)
	  ○ ≥15 to <30kg will receive dupilumab 300 mg or placebo SC every 4 weeks following a loading dose of 600 mg on day 1 (Visit 2)
	  ○ ≥30kg will receive dupilumab 300 mg or placebo SC every 2 weeks following a loading dose of 600 mg on day 1 (Visit 2)
	
	• Participants aged 6-17 years old:
	  ○ ≥15 to <30kg will receive dupilumab 300 mg or placebo SC every 4 weeks following a loading dose of 600 mg on day 1 (Visit 2)
	  ○ ≥30 to <60kg will receive dupilumab 200 mg or placebo SC every 2 weeks following a loading dose of 400 mg on day 1 (Visit 2)
	  ○ ≥60kg will receive dupilumab 300 mg or placebo SC every 2 weeks following a loading dose of 600 mg on day 1 (Visit 2)
	
	• Participants aged 18 years or older will receive dupilumab 300 mg of placebo SC every 2 weeks following a loading dose of 600 mg on day 1 (Visit 2)
	
	Placebo for Study Drug - Route/Schedule
	Placebo matching dupilumab is prepared in the same formulation as the active agent without the addition of protein (i.e., active substance, anti-IL-4Rα monoclonal antibody).
	
	Background Treatment (Cow's Milk Protein) - Dose/Route/Schedule
	Cow's milk protein in powder form for oral use taken daily for 20 weeks: Initial dose at 5 to 20 mg protein daily, escalating every two weeks to 1000 mg daily

Inclusion Criteria	A subject must meet the following criteria to be eligible for inclusion in the study: • Age 4 to 50 years (inclusive) • Subject has a clinical history of allergy to cow's milk or milk-containing foods • Experience clinical reaction at or before 444 mg cumulative protein dose of cow's milk protein on Screening DBPCFC • No clinical reaction observed during the placebo (oat) Screening DBPCFC • Serum IgE to milk of >4 kUA/L within the last 12 months and/or a SPT to milk ≥6 mm compared to a negative control

	• Subjects/Caregivers must be trained on the proper use of the epinephrine auto-injector device to be allowed to enroll in the study. • Subjects with other known food allergies must agree to eliminate these other food items from their diet so as not to confound the safety and efficacy data from the study • Written informed consent from parent/guardian for minor subjects. • Written assent from minor subjects as appropriate (eg, at and above the age of 7 years or the applicable age per local regulatory requirements) • For women of childbearing potential, must agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods (barrier methods or oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy) during the treatment period and for 60 days after the last dose of study drug
Exclusion Criteria	A subject who meets any of the following criteria will be excluded from the study: • Any previous exposure to dupilumab • Known hypersensitivity to dupilumab or any of its excipients • Known hypersensitivity to epinephrine or any of its excipients • Allergy to oat (placebo in DBPCFC) • History of severe anaphylaxis to cow's milk, defined as neurological compromise or requiring intubation • Recent history of frequent severe, life-threatening episodes of anaphylaxis or anaphylactic shock as defined as 3 or more episodes of anaphylaxis within the past year • Inability to tolerate biological (antibody) therapies • Body weight <5 kg at the time of screening • History of eosinophilic esophagitis (EoE), other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia (e.g., difficulty swallowing, food "getting stuck"), or recurrent gastrointestinal symptoms of undiagnosed etiology. • History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension • History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, and hereditary angioedema • Established diagnosis of a primary immunodeficiency disorder (eg, Severe Combined Immunodeficiency, Wiskott Aldrich Syndrome, DiGeorge Syndrome, X-linked Agammaglobulinemia, Common Variable Immunodeficiency), or secondary immunodeficiency • Severe asthma (Global Initiative for Asthma, 2020: Personalized management to control symptoms and minimize future risk requiring treatment Steps 4 or 5; **Appendix 1**) • Mild or moderate asthma (Global Initiative for Asthma, 2020: Personalized management to control symptoms and minimize future risk requiring treatment Steps 1-3; **Appendix 1**), if uncontrolled or difficult to control • Uncontrolled asthma as evidenced by:

	○ Forced expiratory volume in 1 second (FEV1) <80% of predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) <75% of predicted, with or without controller medications (only for age 7 or greater and able to reliably perform spirometry) OR; ○ One overnight admission to a hospital in the past year for asthma OR; ○ Emergency room (ER) visit for asthma within six months prior to screening • Current participation or within the last 4 months in any other interventional study • Use of omalizumab within 6 months prior to screening • In build-up phase of immunotherapy for aeroallergens or venom • Use of other investigational drugs or allergen immunotherapy (eg, oral, subcutaneous (SC), patch or sublingual) or immunomodulatory therapy (not including corticosteroids) within 4 months of participation • Receipt of live vaccine within 2 weeks prior to Study Week 0 or unable to comply with recommendation against receiving live vaccine during study • Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers. • Use of oral antihistamines (within five half-lives), beta-agonists (within 12 hours), theophylline (within 12 hours), and cromolyn (within 12 hours) prior to Screening DBPCFCs or SPTs • Pregnant or breastfeeding women, women planning to become pregnant or breastfeed during the study • Girls at or beyond menarche who are not sexually abstinent and are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 60 days after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence. ○ Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. ○ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and the lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together. • Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may

	interfere with the participant's ability to comply with study requirements, or that may impact the quality or interpretation of the data obtained from the study.

Participant Stopping Rules	Participants may be prematurely terminated from the study for the following reasons:
	• The participant elects to withdraw consent from all future study activities, including follow-up
	• The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed)
	• The investigator no longer believes participation is in the best interest of the participant
	• The participant dies
	• Missing 2 consecutive doses of study drug (dupilumab or placebo)
	• The participant does not tolerate 5 mg milk protein at the initial escalation (Visit 4)
	• Missing ≥7 consecutive days of milk protein OIT therapy (e.g. concurrent illness such as gastroenteritis)
	• Anaphylaxis resulting in hypotension, neurological compromise or mechanical ventilation secondary to OIT dosing or any food challenge
	• The subject develops biopsy-documented eosinophilic esophagitis (EoE) with synchronous symptoms or other eosinophilic gastrointestinal disease
	• Any serious or unexpected adverse event
	• Any subject deemed to have severe allergic reactions and who receives aggressive therapy (e.g., mechanical ventilation, three or more doses of epinephrine for a life threatening reaction) at any time should be discontinued from further therapy
	• Other circumstances including, but not limited to, the following:
	  ○ Poor control or persistent activation of secondary atopic disease (e.g., AD, asthma)
	  ○ Started on beta-blockers, or other prohibited medications, with no alternative medications per the prescribing clinician
	  ○ Pregnancy

Study Stopping Rules	During the course of the study, if the investigator or DSMB discover conditions that indicate that the study should be discontinued, an appropriate procedure for terminating the study will be instituted, including notification of the FDA and IRB or EC (ethics committee). If any of the stopping rules listed below are met, study enrollment will be suspended, the initial dose day will be suspended, dose escalation during build-up will be paused, and all enrolled participants will remain on their current dose pending expedited review of all pertinent data: • Any death related to dosing • More than one participant requiring more than two injections of epinephrine during a single dupilumab injection

	• One case of severe and prolonged anaphylaxis related to milk OIT dosing or oral food challenge that does not respond to 3 doses of epinephrine or that includes intubation
	• More than 2 cases of hypotension related to milk OIT or oral food challenge
	• More than 3 participants require more than 2 injections of epinephrine for anaphylaxis during a single dosing event of milk OIT
	• More than 3 of either of the following events:
	  ○ Severe adverse event, other than anaphylaxis, related to investigational product or
	  ○ Eosinophilic esophagitis with clinical symptoms and confirmatory biopsy findings

LIST OF ABBREVIATIONS

AD	Atopic Dermatitis
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
BAT	Basophil Activation Test
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form (electronic or paper)
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Cumulative Tolerated Dose
DBPCFC	Double-blind, Placebo-controlled Food Challenge
EAACI	European Academy of Allergy and Clinical Immunology (EAACI)
EASI	Eczema Area and Severity Index
EDC	Electronic data capture
EEsAI	Eosinophilic Esophagitis Activity Index
EoE	Eosinophilic Esophagitis
FAQLQ	Food Allergy Quality of Life Questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FPI	Full prescribing information
GI	Gastrointestinal
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IM	Intramuscular
IL-4	Interleukin-4
IL-4Rα	Interleukin-4 Receptor Alpha
IL-13	Interleukin-13
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events

OIT	Oral Immunotherapy
PCSV	Potentially Clinically Significant Value
PEESS	Pediatric Eosinophilic Esophagitis Symptom Score
PFS	Pre-filled Syringe
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SC	Subcutaneous
SCORAD	Scoring Atopic Dermatitis
SOC	System Organ Class
SPT	Skin Prick Test
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
Th2	Type 2 Helper T-Cell
WOCBP	Woman of Childbearing Potential

1. BACKGROUND AND RATIONALE

1.1. Background

Food allergy is a potentially life threatening condition that affects up to 8% of young children and 3 to 5% of the entire US population (Gupta 2018). Similar to many other childhood allergies, milk allergy sometimes persists into adulthood and, along with tree nuts and peanuts, is one of the most common foods that may cause anaphylaxis (Fiocchi 2015, Lifschitz 2015). The current remedies for food allergy are food avoidance and treatment with medications such as injectable epinephrine for accidental exposures associated with severe allergic symptoms. Although recent progress has been made in the treatment of food allergy though allergen-specific oral immunotherapy (OIT), there is an unmet need for a new therapy in food allergy. The aim of OIT is to induce desensitization and increase the threshold for milk ingestion, and reduce the risks of allergic reactions after accidental ingestion; however, many subjects in OIT trials experience dose-related side effects that can hinder their compliance and the overall efficacy of OIT (Vázquez-Ortiz 2013, Martorell Calatayud 2014, Mori 2017, De Schryver 2019). While it is known that allergic response to food is an IgE-mediated event, recent data suggest that the role of interleukin-4 (IL-4) and IL-13 may also play a significant role in food allergy pathogenesis (Noval Rivas 2016, Rial 2019). This clinical study proposes to examine the effect of dupilumab, a monoclonal antibody, which blocks the action of these cytokines, to enhance the safety, tolerability and efficacy of milk protein OIT in subjects with significant allergy to milk.

The immune system in the gut actively induces an immune tolerant state to the proteins that are normally consumed. Food allergy occurs when the body has a break in this tolerance, which results in an abnormal immune reaction to food. Milk allergy is an IgE-mediated hypersensitivity reaction following the ingestion of normally innocuous milk protein. Cross-linking of milk-specific IgE (sIgE) bound to high affinity IgE receptors on mast cells and basophils triggers immediate degranulation, and the subsequent release of a diverse array of inflammatory mediators results in severe allergic symptoms such as hives, wheezing, vomiting and, in severe cases, anaphylactic shock. Release of these mediators also initiates type 2 helper T-cell (Th2) cytokine release, which results in eosinophil infiltration and creates a vicious cycle of chronic allergic inflammation. Like other forms of allergy immunotherapy, OIT to milk involves a slow up-dosing of exposure to allergen over time to desensitize or increase the threshold of reactivity to milk. Once reaching a target level of milk protein, subjects are continued on a maintenance dose of milk protein to maintain desensitization. Although many subjects on a maintenance dose of milk protein have demonstrated desensitization to milk (i.e. the ability to tolerate a level of exposure to milk without an allergic reaction), up to 95% subjects exhibit related adverse events (AEs) during OIT with 40% experiencing gastrointestinal (GI) symptoms (Vázquez-Ortiz 2013, Martorell Calatayud 2014, Mori 2017, De Schryver 2019). While the majority of these are mild and decline with prolonged treatment, approximately 25% of patients experience more severe, unpredictable reactions. Roughly 20 to 30% of patients are unable to complete their up-dosing regimen due to side effects, of which the majority are related to the GI system. In those who do successfully desensitize, an additional issue with current OIT arises, specifically its limited ability to induce clinical tolerance (i.e. the persistence of desensitization after subjects are taken off of OIT) (Keet 2012, Suárez-Fariñas 2019). In many of the studies with milk OIT, despite years of

immunotherapy, subjects lose their tolerance within weeks of halting daily milk intake, with only 50% or fewer patients maintaining a sustained unresponsiveness after 2 months off OIT.

Dupilumab, a fully human monoclonal antibody directed against interleukin-4 receptor alpha (IL-4Rα), blocks the activity of IL-4 and IL-13 at both the type 1 and 2 receptor (Regeneron Pharmaceuticals, Inc. 2019, Sastre 2018). These receptors are present on a majority of the cell types involved in the induction and perpetuation of a Type 2 response, including B cells, eosinophils, macrophages, and basophils, and the binding of IL-4 and/or IL-13 has been shown to initiate a signal cascade that plays a critical role in modulating the expression of genes involved in both IgE class switching and Th2 cell differentiation. This pathway has been implicated in multiple atopic diseases via its ability to induce B Cell isotype class switching to allergen-specific IgE, Th2 cell proliferation, and proinflammatory cytokine production. Inhibiting both IL-4 and IL-13 signaling with dupilumab has demonstrated clinical efficacy in moderate-to-severe atopic dermatitis (AD), persistent, uncontrolled asthma, nasal polyposis, and is currently being investigated in eosinophilic esophagitis (EoE). It is known that oral allergen up-dosing during OIT induces up-regulation of IL-4 and IL-13 as well as other Type 2 inflammatory cytokines and pathway activity, which contribute to dose-limiting side effects of OIT such as GI (nausea, vomiting, diarrhea and abdominal pain), respiratory (wheezing and shortness of breath), and skin (generalized rash, pruritus, and angioedema) symptoms. By inhibiting the activation of IL-4Rα, it is hypothesized that dupilumab may disable a number of signaling pathways involved in the development and progression of allergic responses.

This study will explore whether dupilumab has the ability to enhance immunomodulatory effects of OIT by decreasing Type 2 responses, decreasing production of milk-specific IgE, and potentially increasing the milk-specific IgG4 response, which will result in improved safety and tolerability of OIT up-dosing as well as improved efficacy as determined by the ability to tolerate a higher cumulative dose of milk protein during a double-blind, placebo-controlled food challenge (DBPCFC) after 18 and 24 weeks of therapy compared to placebo. In addition, the study will evaluate whether dupilumab influences known biomarkers important in the allergic response such as a reduction in allergen-specific immunoglobulin sub-class switching to IgE, decrease in basophil activation, and decreased Th2 cytokine levels.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

This protocol has been designed to explore whether dupilumab can decrease the number and/or severity of abdominal-related events, especially eosinophil activation associated with EoE.

1.2. Rationale

1.2.1. Rationale for Investigational Study

This study will investigate whether addition of dupilumab, a fully human monoclonal antibody directed against IL-4Rα, will improve OIT in subjects with milk allergy. This study will seek to demonstrate that addition of dupilumab to milk protein OIT will enhance the safety, tolerability, and efficacy of OIT. This will be determined by assessing whether treatment with dupilumab provides an enhanced ability to tolerate a higher cumulative dose

of milk protein during a food challenge after 18 weeks of treatment compared to placebo when given concomitantly with milk protein OIT and whether treatment with dupilumab allows for more rapid up-dosing of milk during desensitization. The differences in safety and tolerability will be assessed through an evaluation of treatment differences in AEs and study drop-out rates.

OIT has demonstrated efficacy in desensitizing food allergic subjects through the promotion of physiologic changes that result in the suppression of an allergic response to the ingested food antigen (Pajno 2018). Desensitization is defined as the ability to tolerate a higher threshold of food allergen without an allergic reaction, while consuming the food regularly. Successful desensitization has been demonstrated in the majority of patients undergoing milk OIT, with rates of success varying depending on the specific definition of desensitization (i.e. milligrams of protein tolerated) and OIT protocol used.

The first randomized, controlled trial of milk OIT, which including treatment with egg, suggested significantly higher rates of desensitization in those receiving OIT compared to a control group (64% vs. 35%, respectively) (Staden 2007). In the first randomized, placebo-controlled study of milk OIT, patients receiving OIT saw an increase in median OFC threshold from 40 mg to 5140 mg after 13 weeks of treatment with 500 mg milk protein, with 36% of those receiving OIT maintaining their tolerance two months after treatment cessation (Skripak 2008). The milk protein dose was escalated to a median of 7000 mg in an open-label follow-up, resulting in 46% of patients tolerating an OFC of 16,000 mg (Narisety 2009). Recent work by Mori et al. mirrored these positive results, with 73% of children in their cohort reaching complete or partial desensitization (Mori 2017).

Additional research has demonstrated significantly greater rates of desensitization in those receiving 1 to 2 g daily milk OIT following sublingual immunotherapy (SLIT) compared to SLIT alone (70% vs 10%; p=0.002); however, results also indicated the effects of milk OIT may have limited durability, with 40% of patients (intent-to-treat) regaining reactivity after several months of milk avoidance (Keet 2012). Long-term follow-up of both the Keet and Skripak studies additionally highlight the potential limitation in durability, with less than one-third of patients fully tolerating milk 3 to 5 years after the completion of OIT (Keet 2013). Furthermore, despite favorable rates of desenstization, a majority of patients still experience significant AEs, primarily GI-related, during the course of OIT, as outlined in Section 1., with approximately 20-30% unable to complete their up-dosing regimen.

Studies have demonstrated the successful use of omalizumab, a monoclonal anti-IgE antibody, in significantly increasing the threshold of reactivity in milk- and multi-food-allergic patients when used as an adjunct during milk- and multi-food OIT (Wood 2016, Andorf 2018). Through its binding of free serum IgE, omalizumab is hypothesized to decrease mast cell and basophil surface-bound IgE and, thus, decrease degranulation and allergic response following allergen exposure. While results indicate a significant reduction of AEs during OIT in those receiving omalizumab compared to placebo, patients receiving adjunct omalizumab continued to experience OIT-related AEs, the majority of which were GI in nature. Additionally, results have indicated a lack of efficacy in the ability of omalizumab to increase long-term tolerance after OIT is discontinued. Each of these issues highlights the unmet need

for a safer and more reliable adjuct to OIT treatment that enables rapid and long-lasting protection. Dupilumab as an adjunct to daily OIT may meet this need given its additional inhibition of a number of signaling pathways involved in the development and progression of allergic responses beyond its suppression of allergen-specific IgE production.

1.2.2. Rationale for Study Design

Milk protein OIT, with and without dupilumab, will be tested in a 2-arm, double-blind, randomized, parallel-group, study in subjects with confirmed milk allergy. Pediatric subjects will be enrolled as children represent the majority of subjects with milk allergy and are a greater risk for accidental ingestion of milk. Dupilumab/placebo treatment for 16 weeks as an adjunct to 14 weeks of daily oral milk treatment will be evaluated, followed by maintenance period of 6 weeks of daily oral milk treatment with concomitant dupilumab or placebo. Two treatment groups are required to provide informative controls and minimize bias on clinical endpoints: dupilumab plus milk protein OIT and placebo plus milk protein OIT. Subjects will be treated for 16 weeks with either bi-weekly SC dupilumab or placebo. After the first 4 weeks, subjects will begin a 14 week up-dosing regimen of daily oral milk protein OIT. The study will assess an up-dosing regimen up to a maximum of 1000 mg over the following 14 weeks of the study. Subjects who achieve 1,000 mg daily dose of milk protein by week 18 will maintain this dose, as tolerated, following the week 18 DBPCFCs. Subjects not achieveing 1000 mg by week 18 will continue to updose to the target maintenance dose of 1000 mg after the week 18 DBPCFCs until the week 24 DBPCFCs.

This design allows for a direct comparison between adjunct dupilumab plus OIT to placebo plus OIT during the 18-week double-blind treatment period. It will also evaluate the effect of increasing milk protein OIT, defined as an increase in the proportion of subjects who pass a DBPCFC.

1.2.3. Rationale for Dose Selection

1.2.3.1. Dose and Regimen for Dupilumab

A SC dose of 300 mg Q2W was recently approved in the US for treatment of moderate-to-severe AD in adults. Doses of 300 mg Q2W and 300 mg QW were shown to have an acceptable safety profile in adult AD patients in 3 phase 3 studies. In addition, 300 mg Q2W had an acceptable safety profile in a phase 2b study in adults with persistent asthma (Wenzel 2016). Dosing regimens based on age and weight have recently been approved in the US for the treatment of moderate-to-severe AD in those aged 6 to 17 years.

The doses selected for this study are the approved dosing regimens used in the treatment of AD in individuals aged 6 years and older per the full prescribing information (FPI) for Dupixent® (revised 06/2020). Additional dose regiments selected for use in those aged 4 to 5 years are consistent with data derived from previous studies of the treatment of AD and asthma in those under the age of 12 years.

In study R668-AD-1412, children aged 6-17 years received doses up to 4mg/kg QW for 4 doses, where exposures similar to those in adults receiving 300 mg Q2W were achieved. Significant improvements in measures of AD were noted in these children, with an

acceptable safety profile. As with many monoclonal antibodies, weight is the most significant covariate affecting dupilumab pharmacokinetics. The weight-based doses chosen for treatment in this study are chosen such that patients should achieve similar dupilumab exposure in serum to that observed at the Food and Drug Administration (FDA)-approved adult dose for moderate-severe atopic dermatitis (300mg Q2W), based on pharmacokinetic modeling of the data from study R668-AD-1412.

Refer to Section 6.1.1.2. Dosage, Preparation, and Administration for complete description of dupilumab and placebo for dupilumab for this study. Dupilumab will be administered SC in-clinic by trained clinical staff at least 30 minutes prior to the ingestion of the in-clinic milk OIT dose in order to allow for an accurate attribution of AE relatedness to study drug or milk. The administration of the loading dose of dupilumab will allow systemic concentrations to reach steady-state faster. Rapid attainment of target saturating concentrations may yield a rapid clinical response within 4-week period of dupilumab pre-treatment by suppressing Type 2 effector cell function, which is believed to be responsible for the allergic GI side effects of OIT. Dupilumab blockade of IL-4/IL-13 in AD, an immune-driven disease, reduced skin lesions and suppressed at 4 weeks the mRNA expression of genes related to T-cells, dendritic cells, eosinophils, inflammatory pathways, and Th2-inducing chemokines, whereas increases or insignificant decreases were observed with placebo. The correlation between these mechanistic changes and rapid improvement in clinical measures of disease activity, including Eczema Area and Severity Index (EASI) and Scoring Atopic Dermatitis (SCORAD) scores, support a milk protein OIT study design with only 4 weeks of dupilumab SC pre-treatment (Hamilton 2014). Rapid improvements in forced expiratory volume in 1 second (FEV1) and fractional exhaled nitric oxide have also been observed within 4 weeks in dupilumab studies in asthma (Wenzel 2013, Wenzel 2016). The results in other indications suggest 4 weeks of dupilumab treatment significantly suppresses Type 2-mediated responses.

1.2.3.2. Dose and Regimen for Milk Oral Immunotherapy

Concurrent with blinded dupilumab dosing, subjects will begin milk protein OIT beginning at week 4 with an initial daily dose of 10 mg milk protein, escalating to a maximum of 1000 mg protein per day (see **Table 1**). This 1000 mg maintenance dosing regimen has previously been shown to provide significant clinical efficacy and consistent kinetics of the sIgG4 and sIgE response (Keet 2012). The milk protein OIT regimen target of 1000 mg per day may be clinically effective for desensitization for accidental milk exposure (about 1 oz).

2. STUDY HYPOTHESIS/OBJECTIVES

2.1. Hypothesis

We hypothesize that treatment with the IL-4 receptor alpha-chain-targeting antibody, dupilumab, will increase the likelihood of desensitization over the course of 18 weeks and decrease the rate and severity of adverse events associated with cow's milk OIT.

2.2. Primary Objective

To assess whether dupilumab as adjunct to milk oral immunotherapy (OIT) compared to placebo improves desensitization and safety, defined as an increase in the proportion of subjects who pass a double-blind placebo-controlled food challenge (DBPCFC) to at least 2040 mg cumulative milk protein at week 18.

2.3. Secondary Objectives

Clinical

- To assess the effect of dupilumab (compared to placebo) on tolerance of cumulative doses of ≥1040 mg and 4040 mg milk protein at week 18 DBPCFC
- To assess the effect of dupilumab (compared to placebo) on tolerance of cumulative doses of ≥1040 mg, ≥2040 mg, and 4040 mg milk protein at week 24 DBPCFC
- To compare levels of desensitization, defined as an increase in the cumulative tolerated protein dose (log transformed) of milk protein, from baseline to week 18 and baseline to week 24 DBPCFCs across treatment cohorts

Safety

- To compare the rates and severity of OIT-induced gastrointestinal symptoms in subjects receiving dupilumab compared to placebo.
- To compare the safety of each treatment cohort as measured by rate and severity of allergic and non-allergic AEs during respective study phases
- To compare rates of study completion among treatment cohorts

Exploratory and Mechanistic

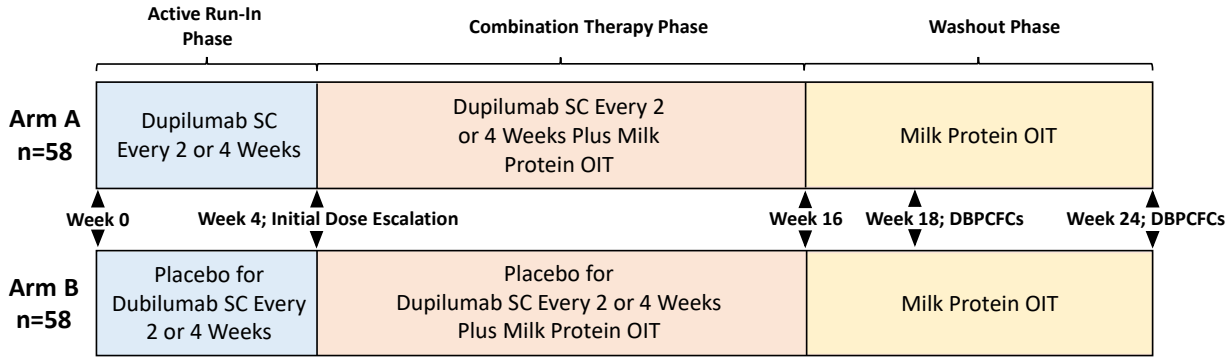
- To explore the relationship between OIT-induced gastrointestinal symptoms and esophageal eosinophilia in subjects receiving dupilumab compared to placebo, if data is available
- To evaluate the immunological responses associated with OIT-induced AEs and successful desensitization

3. STUDY DESIGN

3.1. Study Description and Duration

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, 2-arm study in approximately 116 subjects aged 4 to 50 years, inclusive, who are allergic to cow's milk. The study consists of a screening period and a 24-week treatment period, which includes a 4-week run-in period with dupilumab or placebo followed by 12 weeks of treatment with dupilumab or placebo in combination with a gradual up-dosing of milk protein OIT, then followed by 8 weeks of milk OIT dosing with no dupilumab or placebo (**Figure 1**). The duration of the study is approximately 24 weeks, excluding the screening period.

Figure 1. Study Design of the Phase 2 Study to Test the Efficacy Dupilumab as an Adjunct to Milk OIT



Screening

After obtaining informed consent/assent, subjects will be assessed for eligibility at a screening visit. Procedures for the screening visit may be spread over the course of one to three days; these days do not need to be consecutive and can be spread out over the course of the entire screening window. During screening visits, subjects will be evaluated for the study eligibility criteria.

During screening visits, subjects will undergo double-blind, placebo-controlled, food challenges (DBPCFCs) to confirm milk allergy. The active challenge will consist of 6 doses of milk protein given every 15 to 30 minutes in increasing amounts up to a cumulative total of 444 mg of milk protein. The doses will be 1, 3, 10, 30, 100, and 300 mg. The placebo challenge will consist of placebo material (oat) also given in 6 doses matching that of the active challenge. Both milk protein and oat will be concealed in an age-appropriate, non-offensive food vehicle that aids in masking the taste and appearance.

Before each challenge, the subject will have a physical assessment by a trained clinician of the study team who is blinded to the testing material. All food challenges will be performed under clinician supervision. If the study team suspects a reaction may be developing, they may exercise their clinical judgment to separate doses by up to an additional 30 minutes (1 hour maximum between doses).

Reactions will be scored using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The food challenge will be stopped and appropriately treated when the clinician finds

symptoms and/or signs indicative of two or more objective Grade 1 (Mild) reactions involving two or more organ systems; OR a persistent Grade 1 (Mild) reaction; OR any reaction of Grade 2 (Moderate) or higher severity. After the last dose of each DBPCFC, the subject will be monitored for a minimum of 2 hours and then discharged from the clinic only when deemed clinically stable by a study clinician. Subjects will be considered to have tolerated the DBPCFC and excluded from the study if they do not experience any of the criteria listed above that would result in the stopping of the DBPCFC, including at the highest dose. Additionally, the participant will be excluded if he or she experiences any dose-related AEs at any dose of placebo.

The food challenges can be performed on the same days if no reactions have occurred. If a reaction occurs and is treated, then the challenges should be at least 48 hours apart.

Active Run-In Phase (4 weeks, Visits 2 & 3)

Participants who meet all eligibility criteria at screening will undergo baseline assessments and will be randomized in a 1:1 ratio into one of two cohorts: **Cohort A** will receive dupilumab alone every two to four weeks for 4 weeks, followed by dupilumab every two to four weeks plus milk OIT for 12 weeks, then milk OIT alone for 8 weeks. **Cohort B** will receive placebo for dupilumab alone every two to four weeks for 4 weeks, followed by placebo for dupilumab every two to four weeks plus milk OIT for 12 weeks, then milk OIT alone for 8 weeks.

During the Active Run-In Phase, participants will receive their first dose of dupilumab/placebo in clinic at Visit 2. Participants will receive a second dose of dupilumab/placebo monotherapy at Visit 3 or 4, depending on dose frequency determined by weight and age. Participants assigned to receive dupilumab or placebo every 4 weeks will not undergo Visit 3 as no dose is scheduled at that time.

Combination Therapy Phase (12 weeks, Visit 4 to Visit 10)

Initial Dose Escalation Day (Visit 4)

At week 4 (Visit 4), participants will undergo an initial dose escalation in clinic to determine the dose in which they will begin milk protein OIT. Dupilumab/placebo will be administered in clinic at least 30 minutes prior to the first dose of milk OIT.

The initial dose escalation will consist of three doses of milk protein given every 15 to 30 minutes in increasing amounts up to a cumulative total of 35 mg milk protein. The doses will be 5, 10, and 20 mg milk protein mixed in an age-appropriate, non-offensive food vehicle. The escalation may be stopped and appropriately treated at the occurrence of any AE per clinician discretion. Participants will be discharged with a supply of milk OIT doses for daily home-dosing. The first dose will be taken the day after Visit 4, and the dose at which the participant will begin OIT will be the highest non-cumulative protein dose tolerated during the initial escalation (i.e. 5 mg, 10 mg, or 20 mg). Participants unable to tolerate the 5 mg milk protein during the initial dose escalation will be considered treatment failures.

Combination Therapy (Visit 4 to Visit 10)

During combination therapy (dupilumab/placebo plus milk OIT), participants will return to clinic approximately every two weeks to gradually increase their daily milk OIT dose to a maximum of 1000 mg protein daily as tolerated. Milk OIT will follow a standardized up-dosing regiment (**Table**

1). During combination therapy, dupilumab/placebo will be administered every two to four weeks in clinic at least 30 minutes prior to the in-clinic milk OIT dosing. The last dose of dupilumab/placebo given in the study will be administered at week 16 (Visit 10).

Table 1. Milk Protein OIT Bi-Weekly Up-Dosing Regimen

Dose #	Daily Milk OIT Dose (mg protein)[1]
1	5
2	10
3	20
4	40
5	80
6	160
7	320
8	640
9	1000
[1]Participants may start at dose #1, 2, or 3 depending on dose tolerated during the initial dose escalation	

Week 18 Double-Blind, Placebo-Controlled Food Challenge (Visits 11a and 11b)

At week 18, all subjects will undergo DBPCFCs up to 4040 mg milk protein (cumulative) and placebo to assess desensitization. All food challenges will be performed under clinician supervision. The DBPCFC will consist of 7 doses (milk protein or placebo), given every 15 to 30 minutes: 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg, and 2000 mg protein, resulting in a total challenge of up to 4040 mg milk protein (cumulative). Both milk protein and and oat will be concealed in an age-appropriate, non-offensive food vehicle that aids in masking the taste and appearance. If the study team suspects a reaction may be developing, they may exercise their clinical judgment to separate doses by up to an additional 30 minutes (1 hour maximum between doses). The food challenge will be stopped and appropriately treated in the occurrence of two or more objective Grade 1 (Mild) reactions involving two or more organ systems; OR a persistant Grade 1 (Mild) reaction; OR any reaction of Grade 2 (Moderate) or higher severity. The subject's tolerance to milk allergen, or cumulative tolerated dose (CTD), is defined as the highest cumulative protein dose in which the subject does not experience any of the dose-limiting criteria listed above. The food challenges can be performed on consecutive days if no reactions have occurred. If a reaction occurs and is treated, then the challenges should be at least 48 hours apart.

Participants will receive a new kit of home OIT doses at Visit 11a at the same dose as that previously dispensed and tolerated at Visit 10. Participants will skip their daily home dose of milk OIT on DBPCFC days (Visits 11a and b), but will take their home dose on days between the DBPCFCs if the DBPCFCs are not on consecutive days.

Washout Phase (8 weeks, Visit 10 to Visit 14b)

All participants tolerating 1000 mg daily protein by Visit 10/11a will return to clinic approximately every 2 weeks but will continue to maintain 1000 mg daily, as tolerated. All participants will continue to attempt dose escalations in clinic approximately every two weeks per **Table 1** following the week 18 DBPCFCs until a maximum daily dose of 1000 mg protein, as tolerated.

Those escalating to and tolerating a daily dose of 1000 mg protein daily will remain at that dose for the remaining visits. The final possible up-dosing will occur at Visit 13.

Week 24 Double-Blind, Placebo-Controlled Food Challenge (Visits 14a and 14b)
At week 24, all subjects will undergo DBPCFCs up to 4040 mg milk protein (cumulative) and placebo to assess desensitization. The challenges and procedures are to follow those of the week 18 (Visit 11a and b) DBPCFCs detailed above. The conclusion of the second DBPCFC and Visit 14b will mark the end of the study and no further dosing will occur in participants.

End of study (Visit 14b)
The second DBPCFC at week 24 will mark the completion of Milk OIT Monotherapy phase and end of study (EOS). Participants can exit the trial at Visit 14b to meet the study completion criteria.

3.2. End of Study Definition
The end of study is defined as the last visit of the last subject.

3.3. Planned Interim Analysis
An interim analysis to evaluate the primary efficacy endpoint is planned to occur after the first 40 participants (20 per arm) are enrolled and complete each of their Week 18 DBPCFCs (see **Section 13.8.** for additional details).

3.4. Treatment Failures
A treatment failure will be defined as:
- A participant who does not tolerate 5 mg milk protein at the initial dose escalation
- A participant deemed a treatment failure at any time prior to Visit 14b by the PI

A treatment failure will not receive any further treatment in the study.

3.5. Primary and Secondary Endpoints

3.5.1. Primary Endpoint
- Proportion of subjects treated with dupilumab plus milk protein OIT vs placebo plus milk protein OIT who tolerate at least 2040 mg (cumulative) cow's milk protein during DBPCFC to milk at week 18

3.5.2. Secondary Endpoints

Clinical Endpoints:
- Comparisons of each treatment group for the following:
  - Proportion of participants who tolerate at least 1040 mg cumulative milk protein during DBPCFC at week 18
  - Proportion of participants who tolerate 4040 mg cumulative milk protein during DBPCFC at week 18
  - Proportion of participants who tolerate at least 1040 mg cumulative milk protein during DBPCFC at week 24

  - Proportion of participants who tolerate at least 2040 mg cumulative milk protein during DBPCFC at week 24
  - Proportion of participants who tolerate 4040 mg cumulative milk protein during DBPCFC at week 24
- Change in the cumulative tolerated dose (CTD) of milk protein during DBPCFC from baseline to week 18 and baseline to week 24 across cohorts as pairwise comparisons of all treatment groups.
  - Due to the positive skew for the distribution of the CTD, a log transformation will be applied to reduce the skewness.

Safety Endpoints:

- The rate and severity of OIT-induced gastrointestinal symptoms in subjects receiving dupilumab compared to placebo.
- Proportion of participants who have OIT-induced gastrointestinal symptoms, dupilumab compared to placebo
- The rate and severity of AEs, serious adverse events (SAEs), and safety events in each cohort
- Proportion of participants completing the study among cohorts

Exploratory and Mechanistic Endpoints:

- Change from baseline to week 24 in the log-transformed minimum concentration of milk protein which activates basophils, comparison between dupilumab and placebo
- Percent change from baseline to week 24 in milk-specific and total IgE and milk-specific and total IgG4, comparison between dupilumab and placebo
- Percent change from baseline to week 24 in milk skin prick test (SPT) response, comparison between dupilumab and placebo
- Proportion of subjects experiencing esophageal eosinophilia, dupilumab compared to placebo, if data is available

3.6. Randomization and Blinding/Masking

Subjects will be randomized 1:1 into two cohorts (dupilumab or placebo). **Cohort A** will receive dupilumab every two to four weeks for 4 weeks, followed by dupilumab every two to four weeks plus daily milk protein OIT for 12 weeks, then daily milk OIT alone for 8 weeks. **Cohort B** will receive placebo (for dupilumab) every two to four weeks for 4 weeks, followed by placebo (for dupilumab) every two to four weeks plus daily milk OIT for 12 weeks, then daily milk OIT alone for 8 weeks. A statistician will generate the master randomization lists using randomized block design. Randomization will be stratified by site. The site-specific Master Randomization Assignment Lists are maintained in a secured area (the pharmacy) by the individuals responsible for maintaining the blind (the unblinded pharmacists). Once a patient is eligible for enrollment to the treatment phase of the study (at Visit 0), the unblinded pharmacist will determine treatment cohort for the enrolled participant using the Master Randomization Assignment List and assign a study ID. The unblinded personnel will ensure that the assigned randomization number is in fact the next unused treatment assignment on the site-specific master list. Strict compliance with documentation of randomization procedures is essential to ensure there is a

reliable, verifiable link between the study subject's study ID and the treatment assignment. At the end of the study, the Master Randomization Lists with all randomization numbers and corresponding treatment assignments will be provided to the statistician as a further check on the randomization process.

3.6.1. Blinding

Placebo control and randomization will be the main methods to minimize bias in this trial. DBPCFCs will be performed during screening, at week 18 and at week 24. During the DBPCFC, the order of the milk and placebo (oat) challenges will chosen at random by the unblinded pharmacy personnel, and both the patient and study staff will be blinded to the randomized order of the challenges. Milk powder and its placebo (oat) are both off-white, dry powders and should be difficult to differentiate unless directly compared side by side. An unblinded pharmacist or dietitian designee will mix the milk protein or oat in a food vehicle selected to aid in masking the taste and appearance of the food challenge doses prior to their dispensation for administration in the DBPCFC. To the extent practicable, the same blinded evaluating clinician who determines dose limiting symptoms in the screening DBPCFCs for a participant should evaluate the symptoms in week 18 and 24 DBPCFCs.

Dupilumab and placebo matching dupilumab will be labeled for research purposes in such a way that maintains the blind. Both the active product and placebo are identical in appearance.

3.6.2. Procedure for Unblinding

This is a double-blind study where the participants and the research team involved in the assessment of participants are blinded to the treatment assignments. The pharmacist(s) who maintain the randomization lists are unblinded to the treatment groups.

With the exception of the provisions in **Section 3.6.** and, if circumstances deem necessary, the Data and Safety Monitoring Board (DSMB), this study will remain blinded to all blinded individuals until the prespecified unblinding to conduct the primary analyses. Unblinding the study to conduct the final analysis or study termination will require written approval from the study Sponsor.

Unblinding of treatment assignment for a subject may be necessary due to a medical emergency or any other significant medical event (e.g. pregnancy). If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment
- Only the affected subject(s) will be unblinded
- The designated unblinded pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator
- The investigator will notify the overall PI and/or designee before unblinding the subject, whenever possible

Unblinding must be approved by the study Sponsor unless an immediate life threatening condition has developed, and the study Sponsor is not accessible. The emergency unblinding will also be reported to the DSMB. A full account of the event will be recorded, including the date and time of the unblinding, the reason for the decision to unblind, and the name of the

individual who made the decision and the names of study Sponsor and others who were notified. The reasons for unblinding of a participant's treatment will be included in the final study report. In the case of unscheduled unblinding or the removal of the randomization lists from the secured pharmacy binder, the site PI/study Sponsor must be notified, and a written account of the events must be forwarded to these individuals.

4. SELECTION OF PARTICIPANTS

4.1. Rationale for Study Population

The lower cutoff of 4 years of age was selected to include children where there is some guidance for dosing and to include only participants with sufficient blood volumes to support mechanistic investigations. The upper age limit of 50 years was selected because it is important to study the adult population with cow's milk allergy. The prevalence of food allergy has been increasing over the last 30 years, so a significant number of young adults are food allergic (1 in 10), whereas it is a rarer condition in middle-aged and older adults (Gupta 2019). Our previous studies have not shown age differences in the ability to become desensitized, and it will be important to understand if immune mechanisms related to AE's and desensitization are similar in adults and children.

We anticipate enrolling 116 participants with cow's milk allergy stratified at 2 academic sites in the US. Participants must have either milk specific IgE >4kU/L within the last 12 months or a skin test reactivity of ≥6mm wheal diameter above the negative control to cow's milk. In addition, participants must have a clinical reaction during a DBPCFC to cow's milk protein to establish sensitivity and no clinical reaction during placebo (oat) challenge.

4.2. Inclusion Criteria

A subject must meet the following criteria to be eligible for inclusion in the study:

- Age 4 to 50 years (inclusive)
- Subject has a clinical history of allergy to cow's milk or milk-containing food
- Serum IgE to milk of >4 kUA/L within the last 12 months and/or a SPT to milk ≥6 mm compared to a negative control
- Experience clinical reaction at or before 444 mg cumulative protein dose of cow's milk protein on Screening DBPCFC
- No clinical reaction observed during the placebo (oat) Screening DBPCFC
- Subjects/Caregivers must be trained on the proper use of the epinephrine auto-injector device to be allowed to enroll in the study.
- Subjects with other known food allergies must agree to eliminate these other food items from their diet so as not to confound the safety and efficacy data from the study
- Written informed consent from parent/guardian for minor subjects.
- Written assent from minor subjects as appropriate (eg, at and above the age of 7 years or the applicable age per local regulatory requirements)
- For women of childbearing potential (WOCBP), must agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods (barrier methods or oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy) during the treatment period and for 60 days after the last dose of study drug.

4.3. Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

- Any previous exposure to dupilumab
- Known hypersensitivity to dupilumab or any of its excipients
- Known hypersensitivity to epinephrine or any of its excipients
- Allergy to oat (placebo in DBPCFC)
- History of severe anaphylaxis to cow's milk, defined as neurological compromise or requiring intubation.
- Recent history of frequent severe, life-threatening episodes of anaphylaxis or anaphylactic shock as defined as 3 or more episodes of anaphylaxis within the past year
- Inability to tolerate biological (antibody) therapies
- Body weight <5 kg at the time of screening
- History of eosinophilic esophagitis (EoE), other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia (e.g., difficulty swallowing, food "getting stuck"), or recurrent gastrointestinal symptoms of undiagnosed etiology.
- History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension.
- History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, and hereditary angioedema.
- Established diagnosis of a primary immunodeficiency disorder (eg, Severe Combined Immunodeficiency, Wiskott Aldrich Syndrome, DiGeorge Syndrome, X-linked Agammaglobulinemia, Common Variable Immunodeficiency), or secondary immunodeficiency
- Severe asthma (Global Initiative for Asthma, 2020: Personalized management to control symptoms and minimize future risk requiring treatment Steps 4 or 5; **Appendix 1**)
- Mild or moderate asthma (Global Initiative for Asthma, 2020: Personalized management to control symptoms and minimize future risk requiring treatment Steps 1-3; **Appendix 1**), if uncontrolled or difficult to control
- Uncontrolled asthma as evidenced by:
    - FEV1 <80% of predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) <75% of predicted, with or without controller medications (only for age 7 or greater and able to reliably perform spirometry) or;
    - One overnight admission to a hospital in the past year for asthma or;
    - Emergency room (ER) visit for asthma within six months prior to screening
- Current participation or within the last 4 months in any other interventional study
- Use of omalizumab within 6 months prior to screening
- In build-up phase of immunotherapy for aeroallergens or venom
- Use of other investigational drugs or allergen immunotherapy (eg, oral, subcutaneous (SC), patch or sublingual) or immunomodulatory therapy (not including corticosteroids) within 4 months of participation
- Receipt of live vaccine within 2 weeks prior to Study Week 0 or unable to comply with recommendation against receiving live vaccine during study

- Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers.
- Use of oral antihistamines (within five half lives), beta-agonists (within 12 hours), theophylline (within 12 hours), and cromolyn (within 12 hours) prior to Screening DBPCFCs or SPTs
- Pregnant or breastfeeding women, women planning to become pregnant or breastfeed during the study
- Girls at or beyond menarche who are not sexually abstinent and are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 60 days after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence.
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
    - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and the lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.
- Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements, or that may impact the quality or interpretation of the data obtained from the study.

5. STUDY DESIGN SAFETY CONSIDERATIONS

5.1. Potential Benefits

Although recent progress has been made in the treatment of food allergy through allergen-specific OIT, side effects often limit its full efficacy in many subjects and there is an unmet need for a new therapy in food allergy. It is known that allergic response to food is an IgE mediated event; however, recent data suggest that the role of IL-4 and IL-13 may also play a significant role in food allergy pathogenesis. Consequently, dupilumab treatment, either alone or as an adjunct treatment to OIT, would be expected to provide benefit by blocking the activity of IL-4 and IL-13 and decreasing Type 2 responses, decreasing production of milk-specific IgE, and potentially increasing the milk-specific IgG4 response. It may help in decreasing abdominal pains and risks of EoE. There are no guaranteed benefits to participating in this study. The only possible direct benefit to the participants is, for those participants who develop desensitization as a result of OIT, an ability to decrease their reactions to the offending allergen(s). The likelihood of this is unknown.

5.2. Risk-Benefit of Dupilumab

Please see the most up-to-date package insert for Dupixent (dupilumab). At the time of writing this protocol, dupilumab 300 mg or 200 mg given subcutaneously every two weeks had been approved in the US for the treatment of adults with inadequately controlled chronic rhinosinusitis with nasal polyposis, as well as patients aged 12 years and older with moderate-to-severe AD or moderate-to-severe asthma with an eosinophilic phenotype or that is oral corticosteroid dependent. Since that time, approvals for additional indications or expanded age ranges for existing indications have been added, including the treatment of patients aged 12 years and older with inadequately controlled chronic rhinosinusitis with nasal polyposis; patients aged 6 months or older with moderate-to-severe AD; patients aged 6 years and older with moderate-to-severe asthma with an eosinophilic phenotype or that is oral corticosteroid dependent; patients aged 1 year and older, weighing at least 15 kg, with eosinophilic esophagitis (EoE); adult patients with prurigo nodularis; and adult patients with chronic obstructive pulmonary disease (COPD). Marketing applications are under review in additional countries. Fourteen clinical studies (phases 1 through 3) of repeated-doses of dupilumab in AD patients were completed at the time of writing the initial protocol. Dupilumab has demonstrated robust and consistent efficacy in completed clinical trials, across a variety of clinical outcomes, reflecting clinically meaningful and statistically significant improvement in AD signs, symptoms and quality of life, with sustained efficacy demonstrated to 52 weeks.

Short term (4 weeks), 12- and 16-week treatment with repeated every week (QW) doses of SC dupilumab (75, 150, or 300 mg) monotherapy was well tolerated in adult patients with moderate-to-severe AD not adequately controlled with topical medications. Similar results were observed with dupilumab 300 mg SC QW administered concomitantly with topical corticosteroid (TCS) in study R668-AD-1121.

Dupilumab's efficacy in adult patients with moderate-to-severe uncontrolled asthma has also been demonstrated at doses of 200 mg or 300 mg Q2W for 24 weeks (DRI12544) and 52 weeks (EFC13579). Asthma is a common comorbidity of allergy and asthma exacerbations are an

important safety concern for immunotherapy. In this study, treatment with dupilumab at all doses tested was generally well tolerated with a favorable safety profile.

The first clinical study of dupilumab in pediatric patients aged 6 to <18 years old with AD has been completed. Data generated from this study showed that dupilumab administered as single and repeated weekly doses was generally well tolerated and had an acceptable safety profile similar to that for adults in both pediatric age groups included in this study (6 to 11 years and 12 to <18 years). There were no new safety signals detected with dupilumab in this pediatric population. Most of the AEs reported were mild in intensity, transient in nature and not related to the study drug. Both dose regimens of dupilumab evaluated (2 mg/kg and 4 mg/kg) showed significant clinical benefit in both pediatric age-groups.

Additional trials evaluating the use of dupilumab in pediatric subjects 6 months to 5 years of age with moderate-to-severe AD have been published (AD-1434 & AD-1539). The majority of participants were dosed with dupilumab 300 mg every 4 weeks, with some receiving 200 mg every 4 weeks. The safety profile through Weeks 16 and 52 was observed to be consistent with and similar to that of trials in adults and pediatric patients aged 6 to 17 years with AD. In addition to AEs observed in those 6 years and older, hand-foot-and-mouth disease (5%) and skin papilloma (2%) were reported the evaluated population aged 6 months to 5 years. Efficacy results were consistent with those observed for those aged 6 years and older with moderate-to-severe AD.

The most common adverse reactions (incidence ≥1%) observed in clinical trials are as follows:

- Trials of moderate-to-severe AD (6 months of age and older):
    - Injection site reactions
    - Conjunctivitis
    - Keratitis
    - Blepharitis
    - Eye pruritis & dry eye
    - Oral herpes
    - Other herpes simplex virus
    - Eosinophilia
    - Antibody formation (binding and neutralizing)
    - Hand-foot-and-mouth disease (only observed in studies of those aged 6 months to 5 years)
    - Skin papillomas (only observed in studies of those aged 6 months to 5 years)
- Trials of asthma studies (6 years of age and older)
    - Injection site reactions
    - Oropharyngeal pain
    - Eosinophilia
    - Parasitic (helminth) infection (only observed in studies of those aged 6 to 11 years)
    - Antibody development (binding and neutralizing)

- Trials of chronic rhinosinusitis with nasal polyposis (12 years of age and older)
    - Injection site reactions
    - Conjunctivitis
    - Arthralgia
    - Toothache
    - Gastritis
    - Insomnia
    - Eosinophilia
    - Antibody development (binding and neutralizing)
- Trials of EoE (1 year of age and older)
    - Injection site reactions
    - Upper respiratory tract infection
    - Arthralgia
    - Oral herpes
    - Other herpes simplex virus
    - Antibody development (binding and neutralizing)
- Trials of prurigo nodularis
    - Nasopharyngitis
    - Conjunctivitis
    - Oral Herpes
    - Other herpes simplex virus
    - Dizziness (dizziness postural, vertigo, and vertigo positional)
    - Myalgia (musculoskeletal pain and musculoskeletal chest pain)
    - Diarrhea
    - Antibody development (binding and neutralizing)
- Trials of COPD
    - Viral infection
    - Injection site reactions
    - Nasopharyngitis
    - Rhinitis
    - Keratitis
    - Conjunctivitis
    - Urinary tract infection
    - Eosinophilia
    - Gastritis
    - Headache
    - Back pain
    - Arthralgia
    - Toothache
    - Diarrhea
    - Antibody development (binding and neutralizing)

Rare AEs (incidence <1%) and additional risks include, but are not limited to (see package insert):

- Hypersensitivity reactions, which may include urticaria, rash, erythema nodosum, anaphylaxis, and serum sickness
- Eosinophilic conditions: Eosinophilia, vasculitic rash, worsening pulmonary symptoms, and/or neuropathy
- Thromboembolic complications: Acute myocardial infarction, cerebrovascular accident
- Cholecystitis (only observed in studies of adult patients with COPD)
- Facial skin reactions, which may include erythema, rash, scaling, edema, papules, pruritus, burning, and pain

5.3. Risk-Benefit of Milk Protein OIT

Based on previously published studies, up to 95% subjects exhibit dose-related AEs during milk OIT, the majority of reactions presenting as mild and declining throughout dose escalation (Vázquez-Ortiz 2013, Martorell Calatayud 2014, Mori 2017, De Schryver 2019). Approximately 25% of patients experience more severe reactions. Allergic symptoms may include sneezing, rhinorrhea, urticaria, angioedema, flushing, flares of eczema, ocular, nasal, oral and/or throat pruritus, nausea, vomiting, abdominal discomfort, stridor/laryngeal edema, cough, wheezing and/or shortness of breath, in addition to severe anaphylaxis.

The only major atypical AE reported in the literature related to OIT has been several reported cases of EoE (Hill 2017, Lucendo 2014, Morais Silva 2014). In adult patients with EoE, treatment with dupilumab has shown clinical improvement of symptoms and histology in phase II studies (Sastre 2018).

Oral food challenges may induce a severe life threatening allergic reaction; however, the risk can be greatly mitigated by conducting the challenges in a highly monitored setting and by initiating the challenge with a very small amount of the food, gradually increasing the dose, and stopping the challenge at the first sign of a reaction. If subjects develop an allergic reaction during the challenges, they may need oral, IM, or IV medications. Additionally, IV catheters may be placed, at clinician discretion for any visit, based on factors such as previous reactions, recent clinical history, and clinical status observed at the visit. Trained personnel, including a study clinician, as well as medications and equipment, will be immediately available to treat any reaction. The anticipated rate of life threatening anaphylactic reactions is <0.1%. There may be a risk that during the study subjects may decrease their vigilance against accidental food allergen ingestion because they believe they are protected from it. Therefore, subjects will be warned that they should continue to practice their usual vigilance against accidental ingestion of food allergens or food allergen-containing foods and reminded to carry their epinephrine auto-injector at all times.

The potential benefit of milk OIT to desensitize milk allergic subjects is outlined in **Section 1.2.1.**

5.4. Risk of Other Protocol-Specified Medications

Epinephrine Injection

Common side effects of epinephrine when used properly include anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. Heart problems and stroke, particularly in the elderly

and people with health problems, have been seen. Rare cases of serious skin and soft tissue infections have been reported at the injection site following epinephrine injection in the thigh.

It is very important to use proper techniques when giving epinephrine to avoid injury to the person administering the epinephrine or to the person receiving the injection. In addition to the common side effects above, accidental injection into the finger, hand or foot may result in loss of blood flow to the area causing paleness; coldness; numbness; bruising; bleeding; redness; or damage to the bones. Epinephrine should not be injected into the buttocks and has resulted in cases of gas gangrene.

Anti-histamines

H1 receptor antagonists (e.g., cetirizine, loratadine, fexofenadine) will be used orally according to manufacturer's instructions approximately one hour prior to each food allergen dose at home. The risks of these medications include:

- Central nervous system: Headache, fatigue, somnolence, drowsiness, insomnia, sleep disorders, dizziness, muscle pain
- Gastrointestinal: Diarrhea, nausea, vomiting, dyspepsia, abdominal pain, dry mouth
- Neuromuscular & skeletal: Myalgia, back pain, pain in extremities
- Hypersensitivity reactions (anaphylaxis, angioedema, chest tightness, dyspnea, flushing, pruritus, rash, urticaria)

5.5. General Safety Considerations

- Standing orders from a study clinician will be provided for all clinical study personnel to immediately (i.e. prior to study clinician notification) initiate treatment of reactions, including intramuscular (IM) administration of epinephrine, based on their own clinical judgment.
- A crash cart with pediatric equipment will be available in close proximity of all participant clinic rooms.
- A code team will be available for pediatric and adult patients
- Dosing allergic symptoms and AEs will be captured throughout the study
- Subjects will be prescribed an epinephrine auto-injector (if not prescribed by a treating clinician previous to study entry) and all subjects/caregivers will be trained in its use. Subjects will be advised to carry the auto-injector with them at all times and will have 24-hour access to an emergency contact telephone number
- Subjects/caregivers will be cautioned against consuming any milk or milk-containing foods other than study-supplied food allergen while on study

5.6. Milk OIT Safety Considerations

- All up-dosing visits will be supervised in an in-clinic setting where trained study clinicians are available. Subjects who exhibit moderate or severe allergic symptoms per CTCAE V5.0, or any other symptoms or circumstances per investigator discretion, may have the dose repeated or reduced.
    - For chronic or recurrent GI symptoms, especially upper GI symptoms, investigators are advised to establish a low threshold for instituting a dose repeat or reduction and

for considering early discontinuation of affected subjects from the study due to the potential for eosinophilic esophagitis (EoE).

- Each bi-weekly OIT dosing increase will be administered in-clinic and monitored for adverse allergic events for at least 2 hours prior to discharge.
- Subjects/caregivers will be instructed not to exceed the specifically assigned OIT doses at home. They will also be instructed not to introduce any new foods to the diet and to avoid accidental ingestions.

5.6.1. Guidance for Home Dosing

The subject should take the milk protein dose at approximately the same time each day as part of a meal. Participants should remain awake at least 2 hours after each daily OIT dose to accommodate monitoring. No attempt should be made to make up a missed dose if greater than 6 hours has elapsed from the usual time of dosing.

If moderate or severe allergic symptoms occur during home dosing, the subject or parent/caregiver should call the study site. If moderate or severe symptoms occur after a dose is administered at home, or in the case of any other AE or circumstancce per investigator discretion, the subject may return to the clinic the next day for administration of the next dose under medical supervision.

5.6.2. Missed Milk OIT Doses

If 4 consecutive doses of milk OIT are missed, the subject should return to the clinic for the next dose. If 5 to 6 consecutive doses are missed, the next dose should be administered in clinic at at 50% of the last tolerated dose.

5.7. DBPCFC Safety Considerations

Oral food challenges may induce an allergic response. Allergic reactions can be severe, including life-threatening allergic reactions; however, the risk of an allergic reaction is reduced by initiating the challenge with a very small amount of the food, gradually increasing the dose, and closely monitoring for signs of prespecified challenge-stopping symptoms. If subjects have an allergic reaction during the challenges, they may need oral, IM, or intravenous (IV) medications. Subjects will have an IV catheter placed before the food challenges if they have a medically documented history of anaphylaxis with hypotension requiring IV fluid resuscitation. Additionally, IV catheters may be placed, at clinician discretion for any visit, based on factors such as previous reactions, recent clinical history, and clinical status observed at the visit. Trained personnel, as well as medications and equipment, will be immediately available to treat any reaction. The anticipated rate of life threatening anaphylactic reactions is <0.1%.

5.8. Study Committees

5.8.1. Data and Safety Monitoring Board

The ongoing Stanford Food Allergy DSMB, independent from the study investigators, will provide oversight of subject safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group. If requested, the DSMB may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit

assessment. The DSMB currently provides the Sean N Parker Center for Allergy & Asthma Research with appropriate recommendations on the conduct of the Food Allergy, Asthma, Atopic Dermatitis, Nasal Polyposis and EoE clinical studies to ensure the protection and safety of the subjects enrolled in these studies. All activities and responsibilities of the DSMB are described in the DSMB charter.

6. INVESTIGATIONAL AGENTS

6.1. Investigational and Reference Treatments

6.1.1. Dupilumab (Dupixent®)

Dupilumab will be directly provided by the manufacturer, Regeneron Pharmaceuticals, Inc.

6.1.1.1. Formulation, Packaging, Labeling, and Storage

Please refer to the dupilumab (Dupixent®) FPI for full information on formulation, labeling, packaging, and storage. Dupilumab (Dupixent®) is supplied as the following:

- Dupilumab 150 mg/mL: Each 2.25 mL single-use, prefilled glass syringe with snap-off cap delivers 300 mg of study drug (2.0 mL of a 150 mg/mL solution)
- Dupilumab 175 mg/mL: Each 1.14 mL single-use, prefilled glass syringe with snap-off cap delivers 200 mg of study drug (1.14 mL of a 175 mg/mL solution).

It is a clear to slightly opalescent, colorless to pale yellow solution and should not be used if the liquid contains visible particulate matter or is discolored or cloudy (other than clear to slightly opalescent, colorless to pale yellow). The original PFSs should be stored at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. If necessary, PFSs may be kept at room temperature up to 77°F (25°C) for a maximum of 14 days. Do not store above 77°F (25°C). After removal from the refrigerator, the product must be used within 14 days or discarded. Do not expose the syringe to heat or direct sunlight.

6.1.1.2. Dosage, Preparation, and Administration

Dupilumab will be dosed according to the following algorithm:

- Participants aged 4-5 years old:
  - ≥5 to <15kg will receive dupilumab 200 mg or placebo SC every 4 weeks following a loading dose of 400 mg on day 1 (Visit 2)
  - ≥15 to <30kg will receive dupilumab 300 mg or placebo SC every 4 weeks following a loading dose of 600 mg on day 1 (Visit 2)
  - ≥30kg will receive dupilumab 300 mg or placebo SC every 2 weeks following a loading dose of 600 mg on day 1 (Visit 2)
- Participants aged 6-17 years old:
  - ≥15 to <30kg will receive dupilumab 300 mg or placebo SC every 4 weeks following a loading dose of 600 mg on day 1 (Visit 2)
  - ≥30 to <60kg will receive dupilumab 200 mg or placebo SC every 2 weeks following a loading dose of 400 mg on day 1 (Visit 2)
  - ≥60kg will receive dupilumab 300 mg or placebo SC every 2 weeks following a loading dose of 600 mg on day 1 (Visit 2)
- Participants aged 18 years or older will receive dupilumab 300 mg of placebo SC every 2 weeks following a loading dose of 600 mg on day 1 (Visit 2)

All dose strengths will be removed from their outer box packaging and dispensed in the original PFS as-is. All PFSs will only be used for a single patient. Dupilumab will be dosed a total of 18 weeks as per the randomized arms. Subcutaneous injection sites of the study drug should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations. Used syringes will be discarded per site policy.

6.1.2. Placebo for Dupilumab

Placebo matching dupilumab is prepared in the same formulation as the active product without the addition of protein (i.e., active substance, anti-IL-4Rα monoclonal antibody). Two matching placebo formulations will be used:

- 2 mL placebo matching 300 mg dupilumab formulation
- 1.14 mL placebo matching 200 mg dupilumab formulation

All dose strengths will be removed from their outer box packaging and dispensed in the original PFS as-is. All PFSs will only be used for a single patient. Placebo for will be dosed a total of 18 weeks as per the randomized arms. Subcutaneous injection sites of the placebo should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations. Used syringes will be discarded per site policy.

6.1.3. Milk Powder for OIT

The milk powder for OIT and food challenges, as well as placebo (oat) for food challenges, will be manufactured and provided by the Sean N Parker Manufacturing Facility. See 'Chemistry, Manufacturing, and Controls – Cow's Milk Powder for OIT' for IND# [redacted] for additional information.

6.1.3.1. Formulation, Packaging, and Labeling

The active study product, milk protein, is characterized milk allergen in the form of milk powder. The placebo used is oat flour without milk protein. Please see 'Chemistry, Manufacturing, and Controls – Cow's Milk Powder for OIT' for IND# [redacted] for additional details.

6.1.3.2. Dosage, Preparation, Admistration

Cow's milk powder and placebo (oat) will be provided in unit dose cups and stored as per manufacturer's recommendations at 36°F to 46°F (2°C to 8°C) to maximize stability. Research staff will administer food flour to the participant orally in a non-offending, age-appropriate food vehicle. The vehicles that may be used include applesauce or chocolate or vanilla non-dairy pudding. Dosage will be done per the protocol.

6.2. Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent (dupilumab/placebo and milk OIT), including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed. Following study drug preparation, the pharmacy personnel will keep used dupilumab or placebo for dupilumab boxes (may discard partially used syringes) until monitor reconciliation. All drug material will be released and recorded by the personnel. All records regarding the disposition of the investigational product will be available for inspection.

The participant will be asked to bring back unused OIT doses and study staff will reconcile OIT accountability.

6.3. Assessment of Participant Compliance with Investigational Agent

Participants (and families) will document daily dosing and any reactions from at-home dosing on Dosing & Symptom Diary Logs. For milk OIT-related symptoms, participants will be reminded to report itching of the tongue or mouth; tongue/mouth/throat pain; lip/tongue/throat swelling; stomach pain; nausea/vomiting; nasal itching or congestion; runny nose; and hives around the mouth or face. For specific symptoms related to the study injection, participants will be reminded to report injection site pain, redness, tenderness, and swelling. Parents or caregivers should fill out the diary daily for children less than 12 years old. Children 12 years old and above may fill out the diary themselves with parent or caregiver supervision. Monitoring of compliance will be performed by reviewing the participant's diary and monitoring and counting their returned, unused study product. Unused milk OIT doses will be brought back to the clinic with each visit and collected by study staff for reconciliation of remaining doses.

6.4. Toxicity Prevention and Management

Potential risk of fever, arthralgia, and rash due to biologics (Dupilumab)

Some omalizumab-treated participants have experienced arthritis/arthralgia, rash, fever and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections of omalizumab. These signs and symptoms, similar to those observed in patients with serum sickness due to biologics (monoclonal antibodies), have recurred after additional doses in some patients. Investigational product will be discontinued if a participant develops these signs and symptoms.

Potential risk for eosinophilic conditions

- Subjects will be actively monitored for early development of EoE by monitoring for symptoms at each study visit such as gastroesophageal reflux, nausea, vomiting, abdominal pain, dysphagia, choking or gagging with meals, and food impaction. At Visits 2, 4, 10, and 14a, the validated Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) v2.0 (Franciosi 2011) or Eosinophilic Esophagitis Activity Index (EEsAI) (Schoepfer 2014) questionnaires will be administered to assist with characterization of EoE in children and adolescents or adults, respectively.

- For chronic/recurrent GI symptoms, especially upper GI symptoms, the investigator will refer to a GI specialist for evaluation of suspected EoE when:
  - Any participant withholds OIT dosing for ≥7 days due to GI AEs and is still having GI AEs

- Any participant who develops chronic/recurrent GI AEs as defined by experiencing symptoms for >6 weeks despite dosing adjustments and use of proton pump inhibitors

Potential risk for injection site reactions (ISR) persisting longer than 24 hours
Based on the SC mode of administration as well as a higher incidence of local ISRs observed for dupilumab in general, severe ISRs lasting longer than 24 hours are considered as a potential risk. Any severe ISR that persists longer than 24 hours will be recorded.

Potential risk for drug-drug interactions
The clinical significance of the limited in vitro findings for IL-4 and IL-13 involvement in the CYP regulation reported in the literature, and the impact of dupilumab on CYP enzymes are not fully understood. As a precautionary measure, during the study treatment and up to the end of follow-up, caution should be used for drugs with a narrow therapeutic index that are metabolized via the CYP isoforms. The Investigators are advised to use close clinical observation and/or laboratory monitoring, as applicable, to enable early detection of potential toxic manifestations or lack of activity/efficacy of these narrow therapeutic index drugs, followed by dose adjustment or withdrawal if needed.

Reactions to OIT during the initial dose escalation
Participants may develop symptoms during the initial escalation at Visit 4. A study clinician trained in the protocol will be present on the unit floor. The investigator's judgment will be required to determine the best course of action with possible actions being:

1. Extend time interval between dosing (up to an additional 30 minutes)
2. Discontinue with any further escalation

The escalation may be stopped at the occurrence of any AE per clinician discretion. All subjects will be observed for a minimum of 2 hours following administration of the final dose and will be discharged only when deemed clinically stable by a study clinician.

Reactions to OIT during Combination Therapy or Washout Phase
Participants will undergo physical examination with lung function assessment prior to OIT dose escalation to determine it is safe to escalate the dose. Per investigator discretion and the Manual of Procedures, subjects may be maintained on their current dose of OIT, or down-dose, depending on their tolerance of the current dose and health status. Participants will be observed in clinic following all in-clinic OIT dosing according to the minimum observation periods specified by the Manual of Procedures and discharged only when the participant is deemed clinically stable per the supervising clinician.

If, at any point in the study, the subject complains of new onset vomiting, dysphagia, chronic abdominal pain, and/or difficulty swallowing for more than 2 weeks despite use of daily antacids (https://www.webmd.com/heartburn-gerd/qa/what-are-examples-of-antacids), the subject will be given daily proton pump inhibitors (PPIs) (dosed per age and weight) https://medlineplus.gov/ency/patientinstructions/000381.html and, if no relief occurs in 2 weeks, they will be referred to a gastroenterologist for assessment of possible gastroenterological disorders associated with food allergy (i.e. EoE). If at any point side effects

develop from the use of antacids or PPIs, the subject will be discontinued on the concomitant medication and referred to a GI specialist.

For specific questions related to dosing escalation or continuation of the same dose that are not answered in the above protocol, the Investigator will be available for questions and decision-making.

6.5. Dose Modification

6.5.1. Dose Modification of Dupilumab/Placebo

Dose modification of dupilumab/placebo for an individual subject is not allowed.

6.5.2. Premature Discontinuation of Investigational Agent

Study therapy (dupilumab/placebo and/or milk OIT) will be prematurely discontinued for any participant if:

- the investigator believes that the study treatment is no longer in the best interest of the participant
- the participant has anaphylactic reaction or other severe systemic reaction to dupilumab per investigator decision
- the participant acquires an infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status
- the participant acquires a diagnosis of a malignancy during the study
- the participant demonstrates evidence of pregnancy
- the participant receives treatment with any prohibited concomitant medication or procedure

Study therapy (milk OIT) will be prematurely discontinued for any participant under circumstance that include, but are not limited to, the following:

- poor control or persistent activation of secondary atopic disease (e.g. AD, asthma)
- circumstances (e.g. concurrent illness, such as gastroenteritis, or non-compliance) develop requiring missed allergen OIT dosing of ≥7 consecutive days
- non-adherence with home OIT dosing protocol (excessive missed days per investigator discretion) without consulting with study staff
- the investigator believes that the study treatment is no longer in the best interest of the participant

A decision to discontinue study drug should be discussed with the study Sponsor. The investigator may suspend study treatment at any time if the urgency of the situation requires immediate action and if this is determined to be in the subject's best interest. However, the Sponsor should be contacted as soon as possible in any case of study drug discontinuation.

Subjects who permanently discontinue from study drug and who *do not withdraw from the study* will be asked to return to the clinic for all remaining study visits per the visit schedule.

Subjects who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete an Early Termination visit within 14 days of the last dose of the study drug. Assessments at this visit may include a blood draw for immunological parameters and translational/mechanistic studies; stool/saliva sampling; and physical exam, spirometry (as able), and skin testing.

7. OTHER MEDICATIONS

7.1. Concomitant Medications

Any treatment administered from the time of the first dose of study drug to the final study visit will be considered concomitant medication. This includes medications that were started before the first dose of study drug and are ongoing during the study.

7.1.1. Protocol-Mandated Concomitant Medications

There are no protocol-mandated concomitant or prophylactic medication(s) to be administered during the study.

7.1.2. Permitted Concomitant Medications

All subjects may continue their usual medications, including those taken for asthma, allergic rhinitis, and AD, during the study. Participants may dose with an antihistamine or antacid prior to their home dose; however, they must be able to discontinue antihistamines for at least 5 half-lives prior to the initial day of escalation, skin prick testing, in-clinic OIT updosing, and all oral food challenges. Usual topical steroid use is permitted at the time of skin testing. Systemic (oral, IV, IM) steroid use longer than 7 days at one time or longer than 3 weeks (21 days) duration each year is not allowed. Up-dosing will not occur within 3 days of systemic steroid use. PPI use will be allowed as detailed under *Reactions to OIT During Combination Therapy or Washout Phase*.

7.1.3. Prohibited Medications and Procedures

Participants will be removed from the trial if any of the following medications are used:

- An investigational drug (other than dupilumab as part of the study)
- Immunomodulating biologic agents, including anti-IgE
- Oral antihistamines (within five half lives), beta-agonists (within 12 hours), theophylline (within 12 hours), and cromolyn (within 12 hours) prior to the initial day of escalation, skin prick testing, in-clinic OIT updosing, and all oral food challenges
- Systemic (oral, IV, IM) corticosteroids used for any greater than 7 days at one time or longer than a total of 3 weeks (21 days) duration each year for asthma. If used, subjects must not be up-dosed until at least 3 days after ceasing the administration of oral steroids
- β-blockers

7.2. Rescue Medications

Rescue medications for any clinically significant reaction will include Epinephrine auto-injectors (dosed according to product insert), antihistamine class of medications (dosed according to weight of subject and according to package guidelines), and inhaler medications (short-actingbeta agonist class of medications).The investigators will use their clinical judgment to apply these medications in an event of a reaction. In addition, all rescue medications are available within immediate reach in each room of the research clinic while dosing occurs. Rescue medications can be given IV, IO, IM, by inhalation, and/or by oral route as dictated by the research clinician. For home dosing, the same class of medications will be available and all the

subjects/parents/guardians will receive detailed instructions and education on the use of these reaction medications.

8. STUDY VISITS

8.1. Enrollment

The research study will be explained in lay terms to each potential research participant. The potential participant or guardian of a child participant will sign an informed consent form before undergoing any study procedures, with those aged 7 years or older completeing an assent. Once the informed consent/assent has been signed, the participant is considered enrolled in the study. The purpose of enrollment is to complete the screening phase to determine eligibility. The participant will then be assigned a unique participant number after signing the informed consent/assent document(s).

8.2. Screening/Baseline Visits (V1)

The purpose of the screening period is to confirm eligibility to continue in the study. After obtaining informed consent/assent, subjects will be assessed for eligibility at a screening visit. Procedures for the screening visit may be spread over one to three separate days; these days do not need to be consecutive and can be spread out over the course of the entire screening window. All assessments must be completed no more than 6 months preceding initiation dupilumab/placebo (Visit 2, week 0), excluding the milk-specific IgE value which may be taken from the previous 12 months if needed to establish eligibility. Baseline/screening visit procedures following requirements below but conducted under a different protocol within the past 6 months (or 12 months for milk-specific IgE) prior to Visit 2 can be used towards this study. Visit 1 may occur on the same day as Visit 2, but must be completed prior to any Visit 2 procedure taking place.

The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility and collect baseline data:

- Consent and assent (conducted prior to any screening or study procedure)
- Medical history, including review of all food allergies
- Physical assessment
- Documentation of con meds and AEs
- Epinephrine auto-injector training with Food Allergy & Anaphylaxis Emergency Care Plan
- SPT to cow's milk (only if needed to determine eligibility)
- Lung function (spirometry, or peak flow if spirometry not available, applicable, or able to be performed reliably by the participant). If spirometry and peak flow are both unable to be completed, defer to clinician judgment
- Urine pregnancy test in women of childbearing potential (WOCBP)

Any of the above items may be repeated within the 6 months preceding initiation of study treatment if warranted, in the opinion of the investigator, by changes in the subject's clinical status. After all other eligibility criteria have been met, DBPCFCs to a cumulative 444 mg of milk and placebo (oat)

Double-Blind Placebo-Controlled Food Challenge (DBPCFC) at Screening

Participants meeting all other eligibility criteria will undergo DBPCFC to cow's milk protein and oat (placebo) during screening to confirm an allergy to milk. Randomization of the placebo and

milk challenge order and preparation of the challenge materials will be performed by trained unblinded study personnel.

All food challenges will be performed under clinician supervision. Before each challenge, the subject will have a physical examination and lung function assessment conducted to ensure it is safe and appropriate to conduct the challenge. Each challenge will be supervised by a trained clinician who is blinded to the testing material. The screening DBPCFC will consist of 6 doses of milk protein given every 15-30 minutes in increasing amounts up to a cumulative total of 444 mg protein. The doses will be 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, and 300 mg (see **Table 2**). The other challenge will consist of placebo material given also in 6 matching doses. Vital signs will be assessed every 15 minutes. If the study team suspects a reaction may be developing, they may exercise their clinical judgment to separate doses by up to an additional 30 minutes (one hour maximum between doses). The food challenge will be stopped and appropriately treated in the occurrence of two or more objective Grade 1 (Mild) reactions involving two or more organ systems; OR a persistant Grade 1 (Mild) reaction; OR any reaction of Grade 2 (Moderate) or higher severity. After the last dose of each DBPCFC, the subject will be monitored for 2 hours and then discharged from the clinic. Subjects will be considered to have tolerated the DBPCFC and excluded from the study if they do not experience any of the dose-limiting symptom criteria detailed above and tolerate all doses of the challenge.

Table 2. Dosing Regimen for DBPCFCs at Screening and Weeks 18/24

Dose #	Screening Milk OIT/Placebo Dose (mg protein)	Weeks 18/24 Milk OIT/Placebo Dose (mg protein)
1	1	10
2	3	30
3	10	100
4	30	300
5	100	600
6	300	1000
7	NA	2000

8.3. Active Study Phase Visits

Visits throughout the study will occur every two weeks plus or minus 5 days (i.e. 9 to 19 days apart), excluding the second food challenges at Weeks 18 and 24. The following procedures, assessments, and laboratory measures will be conducted in clinic at each study visit prior to any study product dosing:

- Physical assessment
- Food Allergy Quality of Life Questionnaires (FAQLQ) (only at Visits 2, 11a, and 14a)
  - The applicable versions of the questionnaire will be administered to the participant and guardian for completion as per investigator discretion; these may include:
    - FAQLQ - Child Form (participants aged 8-12 years; Flokstra–de Blok, DunnGalvin 2009)
    - FAQLQ - Teenager Form (participants aged 13-17 years; Flokstra–de Blok 2008)
    - FAQLQ - Adult Form (participants aged 18 years or older; Flokstra–de Blok, van der Meulen 2009)
    - FAQLQ - Parent Form (guardians of participants aged 4-12 years; DunnGalvin 2009)

  - FAQLQ - Parental Burden (guardians of participants aged 4-17 years; Cohen 2004)
- Eosinophilic Esophagitis Questionnaires (only at Visits 2, 4, 10, and 14a)
  - The applicable versions of the questionnaire will be administered to the participant and/or guardian for completion as per investigator discretion; these may include:
    - Pediatric Eosinophilic Esophagitis Symptom Severity Module v2.0 - Parent Report for Children and Teens (Ages 2-17) (Franciosi 2011)
    - Pediatric Eosinophilic Esophagitis Symptom Severity Module v2.0 - Children and Teens Report (Ages 8-17) (Franciosi 2011)
    - Eosinophilic Esophagitis Activity Index (Participants aged 18 years or older) (Schoepfer 2014)
- Lung function (spirometry or peak flow if spirometry not available, applicable, or able to be performed reliably by the participant). If spirometry and peak flow are both unable to be completed, defer to clinician judgment.
- Documentation (and review, when appropriate) of con meds and AEs
- Urine pregnancy test in WOCBP

Active Run-In Phase (Visits 2 & 3, Weeks 0 to 4)

Participants who meet all eligibility criteria at screening will return to clinic at Visit 2. Those continuing to meet eligibility criteria at Visit 2 will be randomized by the site unblinded pharmacist(s) in a 1:1 ratio to begin receiving dupilumab or placebo every two to four weeks in blinded fashion.

Participants will receive their first dose of dupilumab/placebo in clinic at Visit 2. Participants will receive a second dose of dupilumab/placebo monotherapy at Visit 3 or 4, depending on dosing frequency determined by weight and age. Participants receiving dupilumab or placebo for dupilumab every 4 weeks will not return to clinic for Visit 3 as no dosing is scheduled at this time and associated procedures are not applicable.

Dupilumab and its matching placebo will be dosed according to the following algorithm:

- Participants aged 4-5 years old:
  - ≥5 to <15kg will receive dupilumab 200 mg or placebo SC every 4 weeks following a loading dose of 400 mg on day 1 (Visit 2)
  - ≥15 to <30kg will receive dupilumab 300 mg or placebo SC every 4 weeks following a loading dose of 600 mg on day 1 (Visit 2)
  - ≥30kg will receive dupilumab 300 mg or placebo SC every 2 weeks following a loading dose of 600 mg on day 1 (Visit 2)
- Participants aged 6-17 years old:
  - ≥15 to <30kg will receive dupilumab 300 mg or placebo SC every 4 weeks following a loading dose of 600 mg on day 1 (Visit 2)
  - ≥30 to <60kg will receive dupilumab 200 mg or placebo SC every 2 weeks following a loading dose of 400 mg on day 1 (Visit 2)
  - ≥60kg will receive dupilumab 300 mg or placebo SC every 2 weeks following a loading dose of 600 mg on day 1 (Visit 2)

- Participants aged 18 years or older will receive dupilumab 300 mg of placebo SC every 2 weeks following a loading dose of 600 mg on day 1 (Visit 2)

Prior to the first dose of study drug at Visit 2, participants will undergo blood draw and provide a stool/saliva sample (optional). Participants will be monitored for at least 30 minutes following each dose of dupilumab/placebo. Vital signs will be taken prior to dosing and again prior to discharge. Prior to the completion of Visit 2, participants will be trained on a Daily Dosing & Symptom Diary. Participants will be asked to bring their epinephrine auto-injector to each visit throughout the study in order to confirm they are equipped with an injector and that it is not expired. Participants with no injector or an injector that is expired or expiring prior to the next clinic visit will be provided with a prescription for a new epinephrine auto-injector.

Combination Therapy Phase (Visit 4 to Visit 10, Weeks 4 to 16)

Initial Dose Escalation Day (Visit 4, Week 4)

At week 4 (Visit 4), participants will return to clinic undergo an initial dose escalation to determine the dose in which they will begin daily milk protein OIT. As detailed above, the subject will have a physical examination and lung function assessment conducted to ensure it is safe and appropriate to proceed with the escalation. Prior to the first dose of study drug at Visit 4, participants will undergo blood draw. Dupilumab/placebo will be administered in clinic at least 30 minutes prior to the first dose of milk OIT. Vital signs will be taken prior to dupilumab/placebo dosing, and again prior to the start of the initial dose escalation.

The initial dose escalation will consist of three doses of milk protein given every 15 to 30 minutes in increasing amounts up to a cumulative total of 35 mg milk protein. The doses will be 5, 10, and 20 mg protein mixed in an age-appropriate, non-offensive food vehicle (**Table 3**). The escalation may be stopped at the occurrence of any AE per clinician discretion. Participants unable to tolerate 5 mg milk protein during the initial dose escalation will be considered treatment failures.

Table 3. Initial Dose Escalation Regiment

Dose #	Milk OIT Dose (mg protein)
1	5
2	10
3	20

Each participant will be monitored for a minimum of 2 hours following the last dose administered and discharged from the clinic only when deemed clinically stable by a study clinician. Participants will be discharged with a two-week supply of milk OIT doses for daily home-dosing at the highest non-cumulative dose tolerated (i.e. 5, 10, or 20 mg protein) during escalation. The first dose will be taken at home the day after Visit 4, and the participant will return to clinic in two weeks, plus or minus 5 days, to attempt to escalate their daily dose according to **Table 1**. Daily Dosing & Symptom Diary and epinephrine auto-injector training will be repeated prior to discharge.

For all milk OIT doses, the daily home dose should be taken as part of a meal at a consistent time (within 24±2 hours of the previous day's dose), and it is critical to take the dose every day unless otherwise directed. Doses should be separated by at least 12 hours. Vigorous exercise is not permitted for at least 2 hours after the dose of OIT, and there must be at least 1 hour between vigorous exercise and taking the dose. Allergic reactions are still possible when exercise takes place more than 2 hours after the dose. Prior to the completion of Visit 4, participants will be trained on proper epinephrine use (**Appendix 2**).

Combination Therapy (Visit 4 to Visit 10, Weeks 4 to 16)
Following the initial dose escalation (Visit 4), participants will return to clinic every two weeks (±5 days) to gradually increase their daily milk OIT dose to a maximum of 1000 mg protein daily, as tolerated, following a standardized up-dosing regimen (**Table 1**). As detailed above, the subject will have a physical examination and lung function assessment conducted to ensure it is safe and appropriate to proceed with the escalation.

At each visit, participants should return unused OIT doses remaining from the previously dispensed home dosing kit. Prior to the in-clinic dose, accountability should be performed on the returned doses, when possible, and the Daily Dosing & Symptom Diary will be reviewed to assess for AEs and home dosing compliance to ensure the participant meets the criteria for up-dosing. If the participant does not return the unused doses from the previous kit (e.g. they forget the doses at home or the doses are inadvertently lost), review of the Daily Dosing & Symptom Diary is sufficient to evaluate participant compliance. Effort should be made to have the participant return the unused doses at their earliest ability.

Subjects must withhold their daily home dose and any prophylactic antihistamines on the day of the in-clinic dosing but should take all other prescribed medications, except where prohibited in this protocol. Dosing and AEs will be monitored and documented during each in-clinic OIT dosing. The participant will be observed following the in-clinic dose and dispensed a new kit of OIT for home dosing prior to discharge.

During combination therapy, participants in **Cohort A** will continue to receive dupilumab, while those in **Cohort B** continue to receive placebo for dupilumab. Dupilumab/placebo doses will be administered at least 30 minutes prior to the in-clinic milk OIT dosing every two to four weeks. The last dose of dupilumab/placebo given in the study will be administered at week 16 (Visit 10).

Washout Phase (Visit 10 to Visit 14b, Weeks 16 to 24)
The final administration of dupilumab at week 16 will mark the beginning of the washout phase. Daily Milk OIT will be continued alone for 8 weeks, with DBPCFCs conducted at weeks 18 and 24.

Week 18 Double-Blind, Placebo-Controlled Food Challenge (Visits 11a and 11b)
At week 18, under clinician supervision, all subjects will return to clinic to undergo DBPCFCs up to 4040 mg milk protein (cumulative) and placebo to assess desensitization. The DBPCFCs will occur at two separate visits within the span of 7 days. Randomization of the placebo and milk challenge order and preparation of the challenge materials will be performed by trained unblinded study personnel. Both milk protein and and oat will be concealed in an age-appropriate, non-offensive food vehicle to aid in masking the taste and appearance.

At Visit 11a, participants will return unused OIT doses remaining from the previously dispensed home dosing kit. Prior to the DBPCFC, accountability will be performed on the returned doses, when able, and the Daily Dosing & Symptom Diary will be reviewed to assess for AEs and home dosing compliance. Additionally, prior to the first dose of the Visit 11a DBPCFC, a blood draw will be performed.

As detailed above, the subject will have a physical examination and lung function assessment conducted to ensure it is safe and appropriate to proceed with the escalation. Vital signs will be assessed every 15 minutes. Each DBPCFC will consist of 7 doses (milk protein or placebo), given every 15 to 30 minutes: 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg, and 2000 mg protein, resulting in a total challenge of up to 4040 mg milk protein (cumulative). If the study team suspects a reaction may be developing, they may exercise their clinical judgment to separate doses by up to an additional 30 minutes (1 hour maximum between doses). The food challenge will be stopped and appropriately treated in the occurrence of two or more objective Grade 1 (Mild) reactions involving two or more organ systems; OR a persistant Grade 1 (Mild) reaction; OR any reaction of Grade 2 (Moderate) or higher severity. The subject's tolerance to milk allergen, or cumulative tolerated dose (CTD), is defined as the highest cumulative protein dose in which the subject does not experience any of the dose-limiting symptom criteria listed above. After the last dose of each DBPCFC, the subject will be monitored for a minimum of 2 hours and then discharged from the clinic only when deemed clinically stable by a study clinician. The food challenges can be performed on consecutive days if no reactions have occurred. If a reaction occurs and is treated, then the challenges should be at least 48 hours apart.

Participants will be discharged with a new kit of home OIT doses at Visit 11a at the same dose as that previously dispensed and tolerated at Visit 10. Participants will skip their daily home dose of milk OIT on DBPCFC days (Visit 11a and b), but will take their home dose on days between the DBPCFCs if the DBPCFCs are not on consecutive days.

Washout Phase (Non-DBPCFC Visits: Visits 12 and 13)

Participants will return to clinic 2 weeks (±5 days) from Visit 11a for Visit 12, and again in two weeks (±5 days) for Visit 13. Visits 12 and 13 will be conducted in the same fashion and include all procedures as Visits 4 to 10 listed above, excluding administration of dupilumab/placebo. All participants not yet tolerating 1000 mg daily milk protein will continue to attempt dose escalations in clinic at each visit until a maximum daily dose of 1000 mg protein, as tolerated. Those escalating to and tolerating a daily dose of 1000 mg protein daily will remain at that dose for the remaining visits. The final possible up-dosing will occur at Visit 13.

Week 24 Double-Blind, Placebo-Controlled Food Challenge (Visits 14a and 14b)

At week 24, all subjects will undergo DBPCFCs up to 4040 mg milk protein (cumulative) and placebo to assess desensitization. The DBPCFCs will occur at two separate visits within the span of 10 days. Randomization of the placebo and milk challenge order and preparation of the challenge materials will be performed by trained unblinded study personnel. Both milk protein and and oat will be concealed in an age-appropriate, non-offensive food vehicle that aids in masking the taste and appearance.

At Visit 14a, participants will return unused OIT doses remaining from the previously dispensed home dosing kit. Prior to the DBPCFC, accountability will be performed on the returned doses, when able, and the Daily Dosing & Symptom Diary will be reviewed to assess for AEs and home dosing compliance. Additionally, prior to the first dose of the Visit 14a DBPCFC, a blood draw will be performed and a stool/saliva sample will be collected (optional).

As detailed above, the subject will have a physical examination and lung function assessment conducted to ensure it is safe and appropriate to proceed with the escalation. All food challenges will be performed under clinician supervision. Vital signs will be assessed every 15 minutes. The DBPCFC will consist of 7 doses (milk protein or placebo), given every 15 to 30 minutes: 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg, and 2000 mg protein, resulting in a total challenge of up to 4040 mg milk protein (cumulative). If the study team suspects a reaction may be developing, they may exercise their clinical judgment to separate doses by up to an additional 30 minutes (1 hour maximum between doses). The food challenge will be stopped and appropriately treated in the occurrence of two or more objective Grade 1 (Mild) reactions involving two or more organ systems; OR a persistant Grade 1 (Mild) reaction; OR any reaction of Grade 2 (Moderate) or higher severity. After the last dose of each DBPCFC, the subject will be monitored for a minimum of 2 hours and then discharged from the clinic only when deemed clinically stable by a study clinician. The food challenges can be performed on consecutive days if no reactions have occurred. If a reaction occurs and is treated, then the challenges should be at least 48 hours apart.

Participants will be discharged with a new kit of home OIT doses at Visit 14a at the same dose as that previously dispensed and tolerated at Visit 13. Participants will skip their daily home dose of milk OIT on DBPCFC days (Visit 14a and b), but will take their home dose on days between the DBPCFCs if the DBPCFCs are not on consecutive days. At Visit 14b, participants will return unused OIT doses remaining from the home dosing kit dispensed at Visit 14a. Accountability will be performed on the returned doses, when able, and the Daily Dosing & Symptom Diary will be reviewed to assess for AEs and home dosing compliance.

The conclusion of the second DBPCFC and Visit 14b will mark study completion for each participant. Participants can exit the trial at Visit 14b to meet the study completion criteria.

8.4. Unscheduled Visits

All attempts should be made to keep subjects on the study schedule. If disease activity increases or other concerns arise between regularly scheduled visits, participants should be instructed to contact study personnel and may be asked to return to the study site for an “unscheduled” visit.

Unscheduled visits may be performed for significant food allergy episodes which may be reported by the subject between regularly scheduled visits. Unscheduled visits may include, but are not limited to, physical examination, lung function testing, and in-clinic OIT dosing. Review of the

circumstances surrounding the episode and appropriate documentation of the AE will be recorded in the study chart.

8.5. Early Termination Visit

Subjects who are withdrawn from the study prior to study completion (completion of both week 24 DBPCFC visits) will be asked to return to the clinic for an Early Termination visit within 14 days of the last dose of the study drug consisting of end-of-study assessments This visit may include a blood draw for immunological parameters and translational/mechanistic studies; stool/saliva sampling; and/or physical exam, spirometry (as able), and skin testing.

8.6. Schedule of Events

Study assessments and procedures are presented by study period and visit in **Table 4**.

Table 4: Schedule of Events

Study Procedure	**Screening**	**Active Run-In Phase (Dupilumab/Placebo)**		**Combination Therapy Phase (Dupilumab/Placebo + Milk Protein OIT)**						**Washout Phase (Milk Protein OIT)**						
Visit (V)	**V1[1]**	**V2**	**V3[2]**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11a**	**V11b[3]**	**V12[4]**	**V13**	**V14a**	**V14b[5]**
Week (W)	**Within 6 months of V2[6]**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18a**	**W18b**	**W20**	**W22**	**W24a**	**W24b**
Visit Window (d)		**NA**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**V11a + 7d**	**±5d**	**±5d**	**±5d**	**V14a + 10d**
Informed Consent/Assent[7]	X															
Inclusion/Exclusion	X	X														
Medical History/ Demographics	X															
Height/Weight[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[8,9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lung Function[8,10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DBPCFC	X[11]										X	X			X	X
Milk Skin Prick Test	X[12]	X									X				X	
Blood Draw (Mechanistic)[8,13]		X		X							X				X	
Stool/Saliva (Optional)[8]		X													X	
Randomization		X														
Epinephrine Auto-injector Training	X			X												
Daily Dosing & Symptom Diary Training		X		X												
Subject Dosing & Symptom Diary Review[8]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blinded Study Drug Administration[14]		X	X	X	X	X	X	X	X	X						
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Screening	Active Run-In Phase (Dupilumab/Placebo)		Combination Therapy Phase (Dupilumab/Placebo + Milk Protein OIT)						Washout Phase (Milk Protein OIT)						
Visit (V)	**V1[1]**	**V2**	**V3[2]**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11a**	**V11b[3]**	**V12[4]**	**V13**	**V14a**	**V14b[5]**
Week (W)	**Within 6 months of V2[6]**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18a**	**W18b**	**W20**	**W22**	**W24a**	**W24b**
Visit Window (d)		**NA**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**V11a + 7d**	**±5d**	**±5d**	**±5d**	**V14a + 10d**
Food Allergy & Anaphylaxis Emergency Care Plan	X															
Food Allergy Quality of Life Questionnaires[15]		X									X				X	
PEESS or EEsAI Questionnaires		X		X						X					X	
Review Epinephrine Auto-injector[16]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Milk Protein OIT Dispensation[17]				X	X	X	X	X	X	X	X[17]		X	X	X[17]	
Milk Protein OIT Administration				X	X	X	X	X	X	X			X	X		
Unused Milk Protein OIT Accountability[18]					X	X	X	X	X	X	X		X	X	X	X

1. V1 and associated procedures may take place over several visits/days; such visits do not need to be consecutive
2. V3 is only conducted for those receiving dupilumab or placebo for dupilumab every 2 weeks. Those receiving product every 4 weeks do not return to clinic for Visit 3.
3. V11b will be conducted within 7 days of V11a
4. V12 will be conducted two weeks after V11a, plus or minus 5 days
5. V14b will be conducted within 10 days of V14a
6. All screening procedures and results must be completed and obtained within the 6 months preceding V2, excluding milk-specific IgE. If milk-specific IgE results are needed to determine eligibility, such results which must be from the 12 months preceding V2
7. Consent is to be obtained prior to conducting any screening or study procedure
8. When scheduled, these procedures are to be completed prior to study drug dosing (vital signs may additionally continue during and after dosing per protocol)
9. During DBPCFC, initial dose escalation, and any OIT updosing visit, vital signs will be collected every 15 minutes. Vital signs will additionally be taken prior to any dupilumab/placebo dosing and again prior to discharge or in-clinic OIT dosing following dupilumab/placebo dosing. At visits in which a participant will be dosed with 1000 mg and has tolerated the 1000 mg dose at the previous clinic visit, vital signs will be taken prior to dosing and again just prior to discharge at minimum.
10. Spirometry only conducted in those aged 7 years or older and able to perform spirometry reliably. Peak flow acceptable when spirometry unavailable; if both are unable to be performed, defer to clinician judgment
11. Both screening DBPCFCs may be completed in the same visit only if no adverse events occur during the first DBPCFC and time permits

12. At V1, screeners may undergo SPT to milk if no other SPT or milk-specific IgE result exists from the previous 6 or 12 months (for SPT or IgE, respectively) that meet eligibility criteria
13. When scheduled, blood draws include samples for mechanistic studies (including milk-specific and total IgE and IgG4, BAT, and other exploratory tests)
14. On days in which both the dupilumab/placebo and milk OIT are administered in clinic, the dupilumab/placebo will be administered at least 30 minutes before the milk OIT dose. Dupilumab/placebo may be given every 2 or 4 weeks; if given every 4 weeks, Visit 3 will not occur and no injection will be given at Visits 5, 7, and 9.
15. On days in which the Food Allergy Quality of Life Questionnaires are to be completed, the applicable versions of the questionnaire will be administered to the participant and guardian for completion as per investigator discretion; these forms may include those completed by the participant themselves (Child Form, Teenager Form, or Adult Form) and those completed by guardians of food-allergic children (Parent Form and/or Parental Burden Questionnaire).
16. Participant's will be asked to bring their current epinephrine auto-injector to each visit to ensure they are in possession of of an auto-injector and that it is not expired. If needed, the participant will be provided with a prescription for a new epinephrine auto-injector.
17. The doses dispensed to the participant on V11a and 14a for home dosing will be the same dose level as the dose previously dispensed at V10 and 13, respectively. No dose escalation will occur at V11a or 14a.
18. Participants will return unused OIT doses from the home dosing kit dispensed at the previous visit. This accountability should be completed prior to the in-clinic OIT dosing; however, if the participant forgets to return the unused doses or inadvertently discards them, it is acceptable to assess dosing compliance solely through review of the Subject Dosing & Symptom Diary

9. STUDY VARIABLES

9.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, co-morbid atopic conditions, years with food allergy disease, sex, etc.), disease characteristics including medical history, and medication history for each subject.

9.2. Mechanistic Variables

Pharmacodynamic and biomarker variables of interest are:

- *Serum Milk-Specific and Total Antibody Assays (IgE, IgG4)*: The induction of milk-specific IgG4 during OIT has been reported in multiple studies. In some studies, milk-specific IgEs were seen to increase by ~3 fold after 3 months of OIT and gradually return to baseline at one year.
    - In dupilumab studies, dupilumab suppressed both total and allergen-specific IgEs. In general, dupilumab suppresses total IgE by ~ 50% with 12 to 16 weeks of treatment.
- *Basophil Activation Test***:** Basophils are one cell type involved in acute allergic reaction. CD203c has been shown to be increased in basophils from milk allergic subjects compared to non-allergic healthy controls. The utility of the Basophil Activation Test (BAT) was assessed for diagnosing milk allergy in a well-characterized population of milk allergic, milk sensitized and non-sensitized children. The BAT showed high accuracy (97%) in diagnosing milk allergy. In a study of omalizumab in milk allergic subjects, CD203c expression in the BAT decreased during treatment and returned to pre-treatment levels after cessation of treatment (Gernez 2011). However, as a flow cytometry based test, the CD203c MFI reading is intrinsically highly variable. As an improvement to the traditional BAT, the basophil sensitivity test (BST) measures the minimum amount of milk extract required to activate basophils in subject whole blood, as measured by upregulation of CD203c. Basophil sensitivity to other allergens may also be tested.

9.3. Other Exploratory Research & Biospecimen Storage

Blood and esophagial tests may be obtained for additional exploratory tests such as whole blood stimulation and flow cytometry at baseline, 18 weeks, and 24 weeks. Biospecimen storage will occur in the Nadeau laboratory using a previously validated and published storage procedure for samples (available upon request).

10. COMPLETION AND STOPPING CRITERIA

10.1. Individual Subject Stopping Rules

Participants may be prematurely terminated from the study for the following reasons:

- The participant elects to withdraw consent from all future study activities, including follow-up
- The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed)
- The investigator no longer believes participation is in the best interest of the participant
- The participant dies
- Missing 2 consecutive doses of study drug (dupilumab or placebo)
- The participant does not tolerate 5 mg milk protein at the initial escalation (Visit 4)
- Missing ≥7 consecutive days of milk protein OIT therapy (e.g. concurrent illness such as gastroenteritis)
- Anaphylaxis resulting in hypotension, neurological compromise or mechanical ventilation secondary to OIT dosing or any food challenge
- The subject develops biopsy-documented eosinophilic esophagitis (EoE) with synchronous symptoms or other eosinophilic gastrointestinal disease
- Any serious or unexpected adverse event
- Any subject deemed to have severe allergic reactions and who receives aggressive therapy (e.g., mechanical ventilation, three or more doses of epinephrine for a life threatening reaction) at any time should be discontinued from further therapy
- Other circumstances including, but not limited to, the following:
  - Poor control or persistent activation of secondary atopic disease (e.g., AD, asthma)
  - Started on beta-blockers, or other prohibited medications, with no alternative medications per the prescribing clinician
  - Pregnancy

Subjects who are withdrawn prematurely from the study will be asked to complete study assessments, as described in **Section 8.5**.

10.2. Replacement of Subjects

Subjects prematurely discontinued from study will not be replaced.

10.3. Study Stopping Rules

During the course of the study, if the investigator or DSMB discover conditions that indicate that the study should be discontinued, an appropriate procedure for terminating the study will be instituted, including notification of the FDA and IRB or EC (ethics committee).

If any of the stopping rules listed below are met, study enrollment will be suspended, the initial dose day will be suspended, dose escalation during build-up will be paused, and all enrolled participants will remain on their current dose pending expedited review of all pertinent data:

- Any death related to dosing
- More than one participant requiring more than two injections of epinephrine during a single dupilumab injection

- One case of severe and prolonged anaphylaxis related to milk OIT dosing or oral food challenge that does not respond to 3 doses of epinephrine or that includes intubation
- More than 2 cases of hypotension related to milk OIT or oral food challenge
- More than 3 participants require more than 2 injections of epinephrine for anaphylaxis during a single dosing event of milk OIT
- More than 3 of either of the following events:
  - Severe adverse event, other than anaphylaxis, related to investigational product or
  - Eosinophilic esophagitis with clinical symptoms and confirmatory biopsy findings

11. SAFETY DEFINITIONS, REPORTING, AND MONITORING

11.1. Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. AEs that are classified as serious according to the definition of health authorities must be reported promptly (per **Section 11.7**) to the Sponsor. Appropriate notifications will also be made to site principal investigators (PIs), Institutional Review Boards (IRBs), and health authorities, as needed.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice (GCP), and 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

11.2. Definitions

11.2.1. Adverse Event

Any untoward or unfavorable medical occurrence associated with the use of an intervention in humans, whether or not considered related to the intervation (see 21 CFR 312.32(a)). An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE also includes any worsening (i.e. any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

All symptoms or events that occur within two hours and that are expected according to the Investigator's Brochure (milk OIT), package insert (dupilumab), or protocol and related to administration of study drug or oral food challenge will be recorded as a dosing reaction, not an AE; however, episodes in response to home dosing that are Grade 3 or higher per CTCAE V5.0 criteria or that are classified as serious adverse events (SAEs) per **Section 11.2.4.** below, will be recorded on the AE/SAE case report form (CRF) as appropriate.

Any symptom or event that occurs more than two hours after study dosing will be recorded as an AE on the AE CRF but will not be identified as a dosing reaction.

For this study, an AE will include any untoward or unfavorable medical occurrence associated with:

Study therapy regimens:
Dupilumab/Placebo for Dupilumab
In-clinic OIT dosing
Home OIT Dosing

For the study-mandated procedures below, only the signs and symptoms listed under each procedure will be considered outside normal range and will be recorded as an AE. For all other study-mandated procedures, all AEs will be recorded.

Skin Prick Test

The following events related to SPT will be considered AEs if they occur within 48 hours of the SPT:

- Prolonged (>24 hours) pruritus at the SPT site
- Induration/swelling at the SPT site larger than 10 mm in diameter and lasting more than 24 hours
- Allergic or anaphylactic reaction that requires the use of rescue medications, detailed in **Section 7.2**

Blood Draw

The following events related to a blood draw procedure will be considered AEs:

- Syncope/vasovagal events within 30 minutes of the procedure
- Bleeding from the puncture site lasting more than 30 minutes
- Bruising at the puncture site >5 cm in diameter within 24 hours of procedure
- Erythema at the puncture site >5 cm in diameter within 24 hours of procedure
- Allergic reaction to local skin anesthetic that requires rescue medications
- Infection at the puncture site

11.2.2. Suspected Adverse Reaction

Any AE for which there is a reasonable possibility that the investigational drug (dupilumab, and/or milk OIT) caused the AE. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction (SAR) implies a lesser degree of certainty about causality than an AE, which means any AE caused by a drug (21 CFR 312.32(a)).

11.2.3. Unexpected Adverse Event

An "Unexpected AE" or "Unexpected SAR" means an AE or SAR which is considered "unexpected" because it is not listed in the Investigator's Brochure, package insert, or protocol; is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Investigator's Brochure, package insert, protocol, or elsewhere in the current application. Unexpected AEs or Unexpected SARs are further defined in 21 CFR 312.32.

11.2.4. Serious Adverse Event

An AE or SAR is considered "serious" if, in the view of the PI or Sponsor, it results in any of the following outcomes (see 21 CFR 312.32(a)):

- ***Death***: Includes all deaths, even those that appear to be completely unrelated to study drug (e.g. a car accident in which a subject is a passenger)
- ***A life-threatening event*****:** In the view of the investigator, the subject is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- ***In-patient hospitalization or prolongation of existing hospitalization*** (excludes hospitalization for continued observation of allergic reaction for potential of biphasic reaction). In-subject hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a

hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating clinician.

- ***Persistent or significant disability/incapacity*** (substantial disruption of one's ability to conduct normal life functions)
- ***Congenital anomaly/birth defect***
- ***Important medical events*** that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above

Elective or pre-planned hospitalizations for a pre-existing condition or hospital admissions for the purposes of conducting protocol mandated procedures are not considered to be an SAE unless prolonged due to complications.

Injectable epinephrine may be used for both life threatening and non-life threatening allergic reactions. The use of epinephrine will not be considered an SAE if it is used to prevent the progression of non-life-threatening allergic reactions that occur during OFCs (see Section 7.4).

11.2.5. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g. regulators) might also be warranted.

AESIs for dupilumab or placebo in this study include the following:

- Life threatening anaphylactic reactions
- Systemic or extensive hypersensitivity reactions
- Malignancy
- Helminthic infections
- Suicide-related events
- Conjunctivitis (any type or etiology), keratitis or blepharitis (for all these AEs only events that are severe or serious or lasting ≥4 weeks will be reported as AESIs)

AESIs for milk OIT in this study include:

- Life threatening Anaphylactic reactions
- Gastrointestinal AEs resulting in prolonged disruption of dosing; gastrointestinal AEs include dysphagia, nausea, vomiting, abdominal pain, diarrhea, but exclude oral itching/tingling.

11.2.6. Anaphylaxis

The definition of anaphylaxis that has been adopted for this study is from the 2014 position paper by the European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Guidelines Group (Muraro 2007), that was based on the publications of Simons

et al. (2011) and Johansson et al. (2004), and is consistent with the recently published "International consensus on (ICON) anaphylaxis" (Simons 2014). Accordingly, anaphylaxis is defined as a severe, potentially life-threatening systemic hypersensitivity reaction, characterized by being rapid in onset with life-threatening airway, breathing, or circulatory problems that is usually, though not always, associated with skin and mucosal changes.

Clinical criteria for diagnosing anaphylaxis will be as follows (Sampson 2006):
Anaphylaxis is likely when any one of the 3 following sets of criteria is fulfilled:

1. *Acute onset of an illness (minutes to several hours) with involvement of skin and/or mucosal tissue (e,g. generalized hives, pruritis or flushing, swollen lips/tongue/uvula) AND at least one of the following:*
   - Respiratory compromise (eg, dyspnea, stridor, wheeze/ bronchospasm, hypoxia, reduced PEF)
   - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e0g. hypotonia, syncope, incontinence)

2. *Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (miutes to several hours):*
   - Involvement of the skin/mucosal tissue (e.g. generalized hives, itch/flush, swollen lips/tongue/uvula)
   - Respiratory compromise (e.g. dyspnea, stridor wheeze/bronchospasm, hypoxia, reduced PEF)
   - Reduced BP or associated symptoms (e.g. hypotonia, syncope, incontinence)
   - Persistent GI symptoms (e.g. vomiting, crampy abdominal pain)

3. *Reduced BP after exposure to the allergen (minutes to several hours):*
   - Infants and Children: Low systolic BP* (age-specific) or >30% drop in systolic BP
   - Adults: Systolic BP <90 mm Hg or >30% drop from their baseline

   **Low systolic BP for children is defined as less than (70 mmHg + [2 x age]) from 1 to 10 years; and <90 mmHg from age 11 to 17 years*

With respect to the inclusion of being "potentially life-threatening" in the definition of anaphylaxis and how that relates to the assessment of anaphylaxis as an SAE, reference is made to the 2012 FDA Guidance for Industry and Investigators, "Safety Reporting Requirements for INDs and BA/BE Studies," that states, "An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an adverse event or SAR that, had it occurred in a more severe form, might have caused death." Thus, for the reporting of anaphylaxis as an SAE, the severity of the reaction, assessed according to the EAACI system for grading the severity of anaphylactic reactions (Muraro 2007), is also to be taken into account (see **Table 5**).

When the diagnosis of anaphylaxis is made, the basis for having suspected the diagnosis must be documented, using the criteria detailed above.

11.3. Grading and Attribution of Adverse Events

11.3.1. Grading Criteria

The study site will grade the severity of all allergic and non-allergic adverse events, experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Principal Investigator and has been deemed appropriate for the subject population to be studied in this protocol. For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual Events Grade 1 or higher will be recorded on the appropriate AE paper CRF for this study.

Grade 1 = mild adverse event
Grade 2 = moderate adverse event
Grade 3 = severe and undesirable adverse event
Grade 4 = life-threatening or disabling adverse event
Grade 5 = death

In the case that the diagnosis of anaphylaxis is made, the severity of the anaphylactic event will be assessed and staged according to the EAACI system for grading the severity of anaphylactic reactions (Muraro 2007) detailed in **Table 5**.

Table 5. Criteria for Grading of Anaphylaxis Severity

Staging System of Severity of Anaphylaxis	
Stage	**Defined By**
1. *Mild (skin & subcutaneous tissues, GI, &/or mild respiratory)*	Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis
2. *Moderate* (mild symptoms + features suggesting moderate respiratory, cardiovascular or GI	Marked dysphagia, hoarseness and/or stridor; shortness of breath, wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3. *Severe* (hypoxia, hypotension, or neurological compromise) (i.e. Life threatening)	Cyanosis or SpO2 ≤ 92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram, etc.), a treatment-emergent adverse event (TEAE) is defined as an increase in grade from baseline or from the last post-baseline value that does not meet grading criteria. Changes in grade from screening to baseline will also be recorded as AEs but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an AE if changes in therapy or monitoring are implemented as a result of the event/result.

11.3.2. Attribution

The relationship, or attribution, of an AE to the study therapy regimen or study procedures will be determined by the investigator(s) based on all available information and recorded on the appropriate AE/SAE CRF. Final determination of attribution for safety reporting will be determined by the Sponsor.

Table 6. Attribution of Adverse Events

Category	Descriptor	Relationship (to Study Drug or Procedure)
UNRELATED CATEGORY	Not Related	The AE is clearly not related; there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES	Possible	The AE has a *reasonable possibility* to be related; there is evidence to suggest a causal relationship.
	Definite	The AE is clearly related.

11.4. Collection and Recording of Adverse Events

11.4.1. Collection Period

AEs will be collected from the time of consent until a participant completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study. Ongoing AEs at the time of study completion will be followed for 30 days or until the time of resolution, whichever occurs first. SAE information will be collected until the event is considered chronic and/or stable.

11.4.2. Collecting Adverse Events

AEs (including SAEs) may be discovered through any of these methods:

- Observing the participant
- Interviewing the participant (e.g., using a checklist, structured questioning, diary, etc.)
- Receiving an unsolicited complaint from the participant

11.4.3. Recording Adverse Events

Throughout the study, the investigator will record all AEs and SAEs as described previously on the appropriate AE/SAE eCRF regardless of the relationship to study therapy regimen or study procedure. Once recorded, an AE will be followed for 30 days, or until it resolves with or without sequelae, or until 30 days after the participant prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first. Once recorded, an SAE will be collected until the event is considered chronic and/or stable.

11.5. Reporting of Adverse Events and Pregnancy

This section describes the responsibilities of the site investigator to report SAEs, AESIs, and pregnancies to the FDA and the Sponsor. Timely reporting of AEs is required by 21 CFR and ICH E6 guidelines.

Serious Adverse Events and Adverse Events of Special Interest

All SAEs and AESIs, regardless of assessment of causal relationship or expectedness, must be reported by the site investigator to the Sponsor (or designee) within 24 hours of becoming aware of the event. Refer to the Manual of Procedures for the procedure to be followed.

For SAEs and AESIs, all requested information on the SAE CRF will be provided (**Appendix 3**). However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AESI/SAE CRF will be updated and submitted.

Unexpected Non-Serious Adverse Events

An unexpected, non-serious adverse event that is of Grade 2 severity or higher **and** study related will be recorded and reported to the Sponsor under the SAE reporting procedure above (i.e. within 24 hours).

Pregnancy

Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 60 days of the last dose of study drug. A pregnant subject shall be instructed to stop taking study medication. The investigator shall counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject shall continue until the conclusion of the pregnancy and the outcome of each must be reported.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5
- minutes, and 24 hours after birth, if available
- Any abnormalities.

Any complication to pregnancy such as a congenital abnormality or birth defect shall be submitted as an SAE to the sponsor using the SAE reporting procedures described above and to the FDA.

11.5.1. Reporting to the Health Authorities

The Sponsor has the responsibility of reporting all AEs and SAEs to the FDA within the reporting time limits set forth by the FDA.

1. Standard Reporting (IND Annual Report)

This option applies if the AE is classified as one of the following:

- Serious and expected SARs (see **Section 11.2.2**)
- Serious and not a suspected adverse reaction
- Pregnancy

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual IND Report.

2. Expedited Safety Reporting

This category is required if the safety event is classified as one of the following:

a. Serious and unexpected suspected adverse reaction [SUSAR]:

The Sponsor shall report any SAR that is both serious and unexpected. The Sponsor shall report an SAE as a SAR only if there is evidence to suggest a causal relationship between the study drug and the SAE, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

b. Any new findings from studies that suggests a significant human risk

The Sponsor shall report any findings from other clinical, epidemiological studies, pooled analysis of multiple studies, or any finding from animal or in vitro testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure, package insert, or other aspects of the overall conduct of the study.

SUSARs must be reported to the FDA within 15 calendar days; fatal or life threatening events must be reported to the FDA as soon as possible, but no later than 7 calendar days. To report a SUSAR, a finalized, initial SAE case report form and a MedWatch 3500A form will be generated by the site PI.

11.5.2. Reporting to IRBs/IECs

The investigator shall report AEs and SAEs in a timely fashion to their local and central IRB, if applicable, in accordance with applicable regulations and guidelines.

12. CLINICAL MONITORING STRUCTURE

12.1. Site Monitoring Plan

The study monitor and/or designee from Stanford will visit each site prior to enrollment of the first subject, and periodically during the study as per GCP and GMP. Every effort will be made to maintain the anonymity and confidentiality of subjects during this clinical study; however, because of the experimental nature of this treatment, the investigator agrees to allow representatives of the DSMB and authorized employees of the appropriate regulatory agencies and the Sponsor to inspect the facilities used in this study and to inspect, for purposes of verification, the hospital or clinic records of all subjects enrolled into this study.

12.2. Study Monitoring Plan

The investigators will work with the independent DSMB. The DSMB will meet every 6-12 months, or earlier if needed, to review safety data including all reported AEs and SAEs, as well as major and non-major deviations.

12.3. Protocol Amendments

The sponsor (Stanford) may not implement a change in the design of the protocol, assent or ICF without an IRB-approved amendment at Stanford, Mayo, and Phoenix Children's.

12.4. Protocol Deviations

The Sponsor will consider any deviations from the protocol on a case-by-case basis. The investigator or other health professional in attendance must contact the Sponsor as soon as possible to discuss the associated circumstances. The principal investigator (with the DSMB panel if needed) will then decide whether the subject should continue to participate in the study. All protocol deviations and the reasons for such deviations must be noted on the appropriate page of the subject's CRF and recorded on a protocol deviation log (**Appendix 4**).

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice (GCP ICH E6) Sections:

- Compliance with Protocol (Sections 4.5.1, 4.5.2, and 4.5.3)
- Quality Assurance and Quality Control (Section 5.1.1)
- Noncompliance (Sections 5.20.1 and 5.20.2.)

It is the responsibility of the site to use continuous vigilance to identify and report deviations according to the guidelines of the Sponsor. Protocol deviations will be sent to each local IRB/IEC per their guidelines and policies. The site PI/study staff is responsible and adhering to their central IRB reporting requirements.

12.5. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

12.6. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the Sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The Sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any subject within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of subjects required for the study are enrolled earlier than expected

In all cases, the appropriate IRB and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the subjects' interests.

13. STATISTICAL ANALYSIS PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked and unblinded.

13.1. Statistical Hypothesis

The primary efficacy endpoint is the proportion of subjects who tolerate a cumulative dose of at least 2040 mg milk protein during a DBPCFC at week 18. The comparison between the dupilumab plus milk OIT arm (Cohort A) and the placebo plus milk OIT (Cohort B) arm will be made.

Letting p_D (and p_P) be the true proportion of subjects who tolerate a cumulative dose of at least 2040 mg milk protein during a DBPCFC at week 18 in the treatment arms of dupilumab + milk OIT and placebo + milk OIT, respectively. The following hypothesis for the superiority testing will be tested at the 5% 2-sided significance level:

H_0: $p_D = p_P$, i.e. the proportion of subjects who tolerate a cumulative dose of at least 2040 mg milk protein during a DBPCFC at week 18 is the same between dupilumab + OIT arm and the placebo + OIT arm

against the alternative

H_a: $p_D \neq p_P$, i.e. the proportion of subjects who tolerate a cumulative dose of at least 2040 mg milk protein during a DBPCFC at week 18 are different between the dupilumab + OIT arm and the placebo + OIT arm

13.2. Justification of Sample Size

It is assumed that the proportion of subjects who tolerate a cumulative dose of at least 2040 mg milk protein during a DBPCFC at week 18 will be 20%, based on prior data, with the proportion of patients in the dupilumab + OIT arm assumed to be 55%, which is considered to be a clinically meaningful benefit by adding on dupilumab treatment. A sample size of approximately 88 subjects (44 in dupilumab + OIT and 44 in placebo + OIT) will have 90% power to detect the treatment difference of 35% between placebo + OIT and dupilumab + OIT at the 2-sided 5% significance level. Assuming a 25% drop out rate, we will enroll 58 in each arm. The sample size calculations were done by Fisher exact test using SAS (version 9.4, Cary, NC).

13.3. Analysis Sets

13.3.1. Efficacy Analysis Sets

The efficacy analyses will use the intention-to-treat population. The full analysis set (FAS) includes all randomized subjects. Efficacy analyses will be based on the treatment allocated at randomization (as randomized).

13.3.2. Safety Analysis Set

The safety analysis set (SAS) includes all randomized subjects who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAS.

13.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of subjects reflected in the calculation (n), mean, median, first quartile (Q1), third quartile (Q3), standard deviation, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

All data will be summarized by treatment groups as outlined below: Placebo plus milk protein OIT vs dupilumab plus milk protein OIT.

13.5. Efficacy Analyses

Efficacy analyses will be conducted using the FAS population.

13.5.1. Primary Efficacy Analysis

The primary endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization stratification factor (study site) to assess the treatment difference in the proportion of responders in the FAS. Estimate of treatment difference, p-value, and the 2-sided 95 % confidence interval will be calculated.

If a subject withdraws from study, the subject will be counted as a non-responder at time points after study withdrawal. The subject will also be considered a non-responder at the time point when data are missing. All observed data will be used for primary analysis.

Sensitivity analyses utilizing alternative methods for handling missing data will be performed to assess the robustness of the primary analysis result. Alternative methods may include complete case analysis (observed value analysis). Details will be specified in the statistical analysis plan (SAP).

13.5.2. Secondary Efficacy Analysis

Change in the cumulative tolerated dose of milk protein during a DBPCFC from baseline at week 18 and separately week 24 will be analyzed using analysis of covariance (ANCOVA) with treatment as the main effect, stratification variable (study site) and baseline tolerated cumulative amount of milk protein DBPCFC as covariates. In addition, a non-parametric analysis using the Van Elteren test will be conducted to assess the sensitivity to the assumption about normality of response variable as required by ANCOVA.

No imputation will be applied for the missing data for continuous endpoints at week 18, while every effort will be made to reduce the number of missing values. Sensitivity analysis using last observation carried forward (LOCF) will be conducted to assess the robustness of the result, with regard to handling of missing data. Other sensitivity analyses may be conducted and will be specified in the SAP.

For continuous endpoints at week 18 or week 24, the LOCF will be used to impute missing values from subjects who do not achieve 1000 mg daily milk protein at week 24 or early discontinued from study before week 24. No imputation will be applied for the missing data from other subjects.

All secondary endpoints will be analyzed descriptively at given visits. These descriptive analyses may include statistical tests depending on the type of data in the same way as described above.

13.5.3. Exploratory Efficacy Analysis

All exploratory efficacy endpoints will be analyzed descriptively at given scheduled visit if applicable. These descriptive analyses may include statistical tests depending on the type of data. No multiplicity will be done for the exploratory efficacy analyses

13.5.4. Multiplicity Considerations

The overall Type-1 error rate of 0.05 (2-sided) will be controlled for the primary endpoint and the first secondary endpoint (ie, change in the cumulative tolerated dose [log transformed] of milk protein during a DBPCFC from baseline to week 18) using a hierarchical testing procedure. Inferential conclusions about the first secondary endpoint require statistical significance at the 2-sided 0.05 significance level of the primary endpoint.

13.5.5. First-Step Analysis

A first-step analysis may be performed when the last subject completes 24 weeks of the treatment period as specified in the protocol. No changes in the conduct of the study will be made based on this first-step analysis. The assessment of primary and secondary endpoints up to week 24 and performed during the analysis will be the final analysis of the primary endpoint and the secondary endpoints up to week 24. Hence there will be no need for alpha adjustment due to the first-step analysis. If a decision is made to perform the first-step analysis, in order to maintain study integrity with respect to the washout phase and the post-treatment follow-up visits, and analyses, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the first-step analysis and all related activities, restrict other clinical team members and other sponsor personnel from access to individual subject treatment allocation and site level analysis results, and ensure that the dedicated team will not participate in the data review or data decisions for the following post treatment analyses. However, the dedicated team can participate in the analysis following the final database lock.

13.6. Safety Analysis

13.6.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the day from first dose of study drug to the end of the study.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Analysis

All AEs reported in this study will be coded using the currently available version of the CTCAE. Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all AEs by treatment group will include:

- The number and percentage of subjects with at least 1 AE by SOC and PT
- AEs by severity, presented by SOC and PT
- AEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs, as well as AEs leading to permanent treatment discontinuation, will be listed and summarized by treatment group.

13.7. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The baseline assessment will be the latest, valid pre-first-dose assessment available

General rules for handling missing data (for assessments other than efficacy):

- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (e.g. month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, vital sign data, or physical examination data will be made.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with nonprotocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

Statistical considerations surrounding the premature termination of a study:

- If the study is terminated prematurely, only those parameters required for reporting to regulatory authorities will be summarized.

13.8. Interim Analyses

Interim analyses to investigate the primary efficacy endpoint are planned after the first 40 participants (20 per arm) are enrolled and complete their Week 18 DBPCFCs. The interim analysis is designed to allow for early stopping when we reject the null hypothesis with a significant difference in the proportions of participants who tolerate a cumulative dose of at least 2040 mg

milk protein during the Week 18 DBPCFCs between the two treatment arms. The O'Brien-Fleming decision boundary is used to control the overall type I error probability at the conventional 0.05 level. The Lan-DeMets error-spending approach that approximates O'Brien-Fleming is used to determine the alpha with the information fraction of 45.5% (40 out of 88 participants). At the interim analysis stage, the null hypothesis will be rejected if the test is significant at the alpha level of 0.002 with an associated absolute Z statistic of 3.13. Thus, the trial will be stopped if the test statistic is less than or equal to -3.13 or greater than or equal to 3.13 with a p value ≤ 0.002; otherwise, the null hypothesis will be accepted and the trial will be continued.

14. DATA MANAGEMENT

Study center personnel will complete individual source documents or CRFs in black or blue ink. All corrections to entered data will be made by drawing a single line through the information to be corrected. All corrections will be initialed and dated. Personnel will not use “white-out” or obscuring correction fluid/tape. A final CRF will be prepared for each subject within 14 days from the study termination. A CRF is required for every subject who received any amount of test drug.

The investigator will retain a copy of all files pertaining to this study for 2 years following the completion of the study or longer, if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality. If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

14.1. Data Capture Methods

Data will be captured using source document templates and then entered into the electronic data capture (EDC) system, Redcap. The study personnel will enter the data into the EDC, and the study investigator will review data for accuracy, completeness and accurate documentation.

14.2. Types of Data

Data collected includes, but is not limited to, demographics, physical exam information, vital signs, food challenge results, total and specific IgE and IgG4, adverse events, concomitant medications, dose escalations home diary reviews and adverse events. The EDC should be completed within 10 days of each visit.

14.3. Source Documents and Access to Source Data/Documents

Each site will maintain medical and research records for this trial including source documents and CRFs, in compliance with ICH-GCP, local and national regulatory requirements for the protection of confidentiality of subjects. Source data includes original records of clinical finds, observations, or other activities relevant to the clinical trial. These can include, but not limited, to hospital records, clinical and office charts, laboratory notes, subjects’ diaries, recorded data from automated instruments, x-rays, pharmacy records, and laboratory records.

Approved study staff will have access to subject records. Further, as required by law or other regulations, the IRB and FDA will have access to the study records.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Good Clinical Practice Statement

The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever affords the greater protection to the subject.

15.2. Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study, dupilumab/placebo dosing, and milk protein dosing procedures and risks are given to the subject and written documentation of informed consent is required prior to starting study agent/intervention. Consent forms will be IRB approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The subject may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subject for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.2.1. Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or study staff will review the consent and answer questions with the potential participant and must sign the consent form with the participant and document the informed consent process. For minors participating in this study, informed consent will be obtained from their parent(s) or legal guardian(s). Minors participating in this study will provide assent if they are capable. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

15.3. Assent of Informed Consent Process (in Case of Minor)

A separate IRB-approved assent form, describing (in simplified terms) the details of the study, dupilumab/placebo dosing, and food protein dosing procedures and risks will be used. Assent forms will not substitute for the consent form signed by the subject's legally authorized representative.

15.4. Subject Confidentiality

By conducting this study, the investigator affirms that all study results and information furnished will be maintained in strict confidence. Such information will be communicated to the investigator's review committee under an appropriate understanding of confidentiality.

A published summary of the results of this study is not inconsistent with the preceding affirmation of confidentiality. Any formal publication of data collected as a result of this study will be considered a joint publication by the investigator and the appropriate personnel.

15.5. Study Discontinuation

In the event that the study is discontinued, we will not continue therapy.

15.6. Other

Subjects may withdraw with or without medical advice, or if it is determined that the subject is non-compliant. Withdrawal of the subject will not impact upon future care of any subjects at the Stanford University Hospital or other sites.

16. PUBLICATION POLICY

Following completion of the study, the investigator may publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

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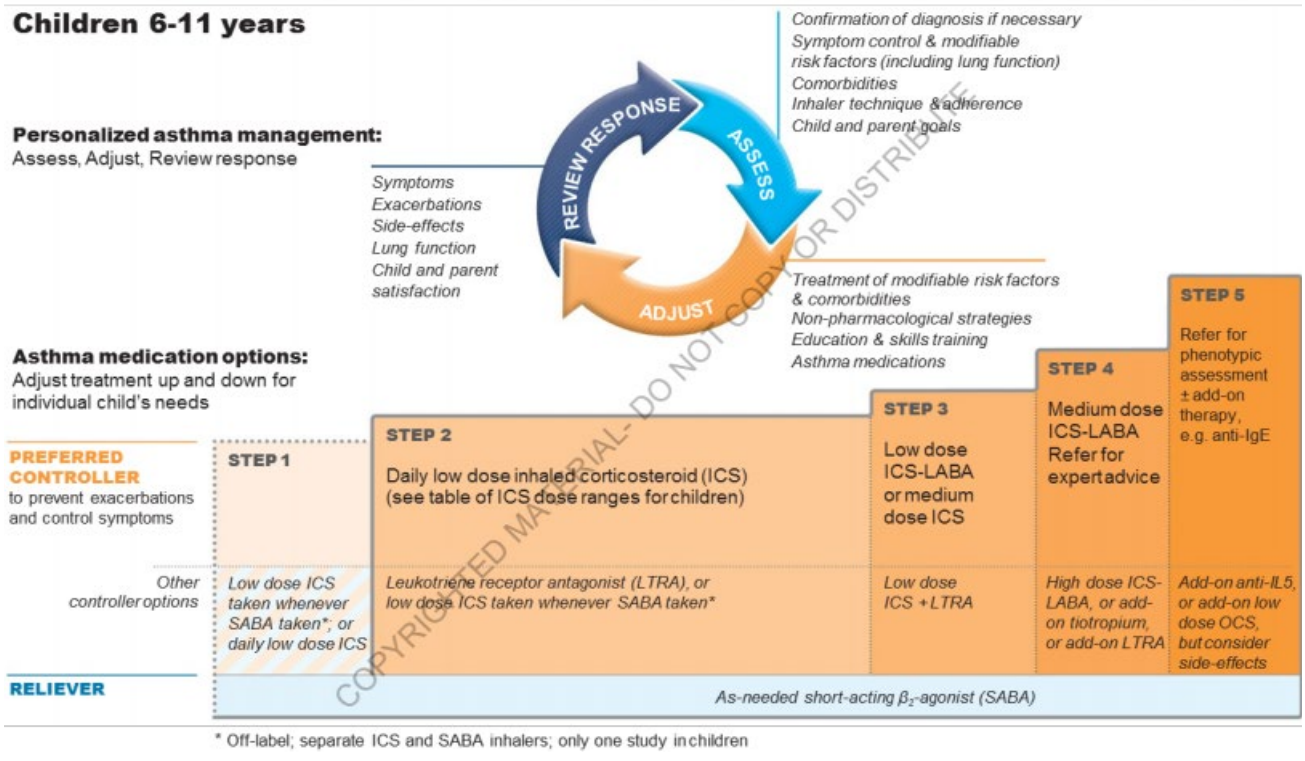
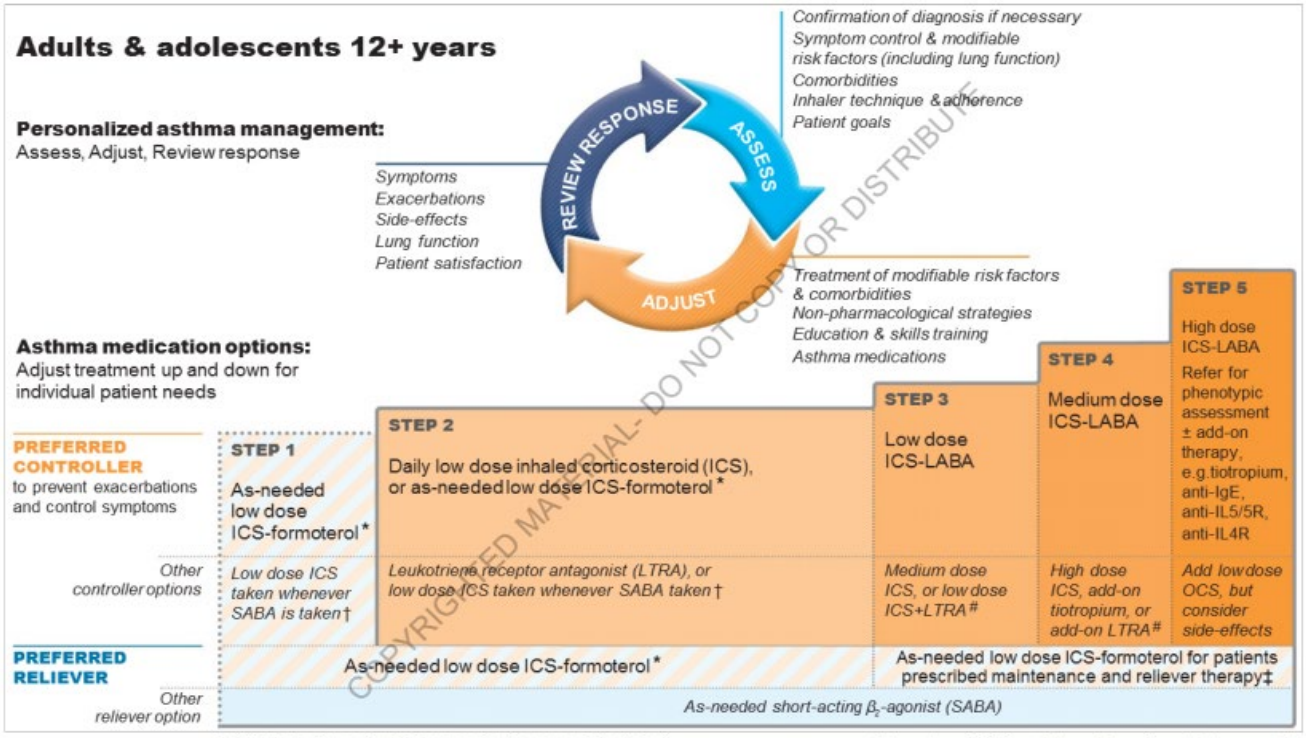
APPENDIX 1. GINA 2020: PERSONALIZED MANAGEMENT FOR ADULTS, ADOLESCENTS, AND CHILDREN TO CONTROL SYMPTOMS AND MINIMIZE FUTURE RISK



* Off-label; separate ICS and SABA inhalers; only one study in children



* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted

APPENDIX 2. INJECTABLE EPINEPHRINE TRAINING FORM

Injectable Epinephrine Training Form

By signing the Injectable Epinephrine Training Form, I acknowledge being appropriately trained and demonstrate understanding in the use and proper storage of Injectable epinephrine and have read the accompanying directions for use (instructions).

Current Wt: _____kg ☐ **Injectable Epinephrine** ☐ **Injectable Epinephrine Junior**

ANAPHYLAXIS INFORMATION (All boxes must be checked)

- ❑ Reviewed epinephrine pictogram with subject and/or family
- ❑ Subject and/or family given an Food Allergy Action Plan with a verbal review to ensure understanding
- ❑ Subject and/or family given information on how to purchase medical identification jewelry tag (e.g. MedicAlert bracelet)

_____ _____

Signature of Adult Participant Date

_____ _____

Signature of LAR (Parent, Guardian or Conservator) Date

_____

Authority to act for participant

_____ _____

Signature of Trainer Date

_____

Printed Name of Trainer

APPENDIX 3. SERIOUS ADVERSE EVENT FORM (SAMPLE)

Serious Adverse Event Form

Date of Report: _____

MM/DD/YYYY

□ Initial Report

□ Follow-up Report *(if follow-up complete participant identification and then only enter new/revised information)*
Initial Report Date: _____

MM/DD/YYYY

Reason for SAE designation *(check all that apply)*:	
□ Death _____ MM/DD/YYYY	□ Congenital anomaly or birth defect
□ Hospitalization or prolonged hospitalization Date of admission/prolongation : _____	□ Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
□ Important medical event	□ Life Threatening event
	□ Form used for other than SAE _____ (e.g. unexpected, related > Grade 2 AE or pregnancy

Event Description	
Date of SAE: _____ MM/DD/YYYY	Date site became aware of the SAE: _____ MM/DD/YYYY
SAE Event Term (Diagnosis) and/or Symptoms	

Describe clinical course of events (include subject's status in the study, how you became aware of the event, and relevant chronology):
Other relevant information: including:
Pre-existing medical conditions (or attach Medical History CRF) (attach additional pages if necessary)
Concomitant medications: (or attach Concomitant Medication Log) attach additional pages if necessary)
Tests, and laboratory data relevant to the event: (attach additional pages sheet if necessary)

<table>
<tr><td colspan="3">Relation to the Study:</td></tr>
<tr><td>Study Medication:_____

□ Unrelated

□ Possible

□ Definite</td><td>Study

Medication:_____

□ Unrelated

□ Possible

□ Definite

□</td><td rowspan="2">If Unrelated to Study Medications Complete the following:

<u>Possible Alternative Etiology</u>:

□ Concomitant medication:

_____

□ Concurrent illness:
_____

□ Study Procedure/Rescue medication:
_____

□ Other possible cause:
_____</td></tr>
<tr><td>Date and time of last dose

_____ _____

MM/DD/YYYY Time (or est)</td><td>Date and time of last dose

_____ _____

MM/DD/YYYY Time (or est)</td></tr>
<tr><td colspan="3">Expectedness (An adverse event is considered “unexpected” when its nature, severity or it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the IND (if applicable).</td></tr>
<tr><td colspan="3">□ Yes □ No</td></tr>
<tr><td colspan="3">Please provide additional discussion:</td></tr>
</table>

<table>
<tr><td>Action taken: Describe action taken in regard to Investigational Product (s) and the management of the event)</td></tr>
<tr><td>attach additional pages, if needed)</td></tr>
</table>

Outcome of Event
□ Resolved, no residual effects; date □ Resolved with sequelae; date: List Sequelae : _____ □ On-going □ Death Was a death certificate obtained? □ No □ Yes Was autopsy obtained: □ No □ Yes, findings relevant to the relationship of the event_____

_____ _____

Name and Signature of Principal Investigator Date

APPENDIX 4. PROTOCOL DEVIATION FORM (SAMPLE)

PROTOCOL DEVIATION REPORTING FORM

Instructions: Any noncompliance with the study protocol, Good Clinical Practice (GCP), or protocol specific Manual of Procedures (MOP) is considered a protocol deviation. Each protocol deviation of **any** nature or severity should be documented. Generally, one form should be used for each deviation. However, if one deviation impacted more than one subject and the effect was the same for each subject, then list all subjects on one form. Once completed and signed, the form is sent to the STANFORD Project Manager

Subject ID:	**Report Date**
Deviation date:	**Date Site Staff became aware of Deviation**:
1.**Description of Deviation** *(attach continuation form, if needed)* :	
2. **Circumstances explaining /contributing to the deviation** *(attach continuation form, if needed)*:	
3. **Effect of Deviation on SAFETY or RISK from study participation**: ☐ No effect ☐ Safety concern or increased risk Explain why the deviation has (or has not) an effect on subject's safety or risk from study participation. In case that deviation has an effect please provide extent of potential safety impact. **Note:** if the deviation resulted in an AE/SAE; major deviation *(attach continuation form, if needed)* :	

4. **Effect of Deviation on the study endpoints or quality of study data**:

☐ No effect ☐ Potential effect on data quality

Explain why deviation has/has not had an effect on the quality of study data. In case that deviation has an effect please provide extent of potential effect on data quality major deviation *(attach continuation form, if needed* :

5. **Corrective action(s) to resolve this Deviation** *(attach continuation form, if needed)*:

6. **Corrective action(s) to prevent similar occurrences** *(attach continuation form, if needed)* :

7. **Participant(s) will continue as a study subject(s)**: *(attach continuation form, if needed)*

YES ☐ NO ☐ Justification:

8. **Notifications**

	Date Notified
STANFORD Project Manager	
Independent Medical Monitor (if applicable)	
IRB (if applicable)	

9. **Was continuation form used?**

YES ☐ NO ☐

_____	_____	_____	_____
Principal Investigator	Date	Independent Medical Monitor *(if applicable)*	Date

For STANFORD Use

Major Deviation *(as determined by the STANFORD Project Manager)* YES ☐ NO ☐

_____	_____
Project Manager	Date

Subject ID: Report Date

PROTOCOL DEVIATION REPORTING FORM CONTINUATION PAGE (do not submit if not used)